A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PHASE 2B STUDY TO EVALUATE THE EFFICACY, SAFETY, TOLERABILITY, AND PHARMACOKINETICS OF ASN002 IN SUBJECTS WITH MODERATE TO SEVERE ATOPIC DERMATITIS

PROTOCOL ASN002AD-201
IND # 133693

FINAL, VERSION 3.0
07 February 2019

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PROTOCOL VERSION HISTORY

Version	Rationale for amendment	Main changes to the protocol
1.0 / 29 March 2018	Initial version	N/A
2.0 / 26 June 2018	-To revise the contact information on the cover page.	-Cover page, sponsor contacts were revised and the name of local medical monitor, email address, telephone number, and fax number were added for the US/Canada medical monitor.
	-To update the restriction of emollient use prior to each study visit.	-Synopsis (inclusion criterion #9), Section 5.1 (inclusion criterion #9), and Section 6.4.1., the restriction of emollient use prior to each study visit was modified and specific timing was removed. No emollient is allowed the day of each visit, before the visit.
	-To add phototherapy as exclusion criteria.	-List of Abbreviation, Synopsis, Section 5.2, and Section 6.4.2., the following exclusion criteria were added and corresponding sections were revised accordingly: "Subject has received any UV-B phototherapy (including tanning beds) or excimer laser within 4 weeks prior to Day 1. Subject has had psoralen-UV-A (PUVA) treatment within 4 weeks prior to Day 1."
	-To revise the exclusion criterion related to prior use of SYK or JAK inhibitor	-Synopsis and Section 5.2, to clarify the exclusion criterion related to prior use of SYK or JAK inhibitor to restrict only the systemic products.
	-To update the Schedule of Events to clarify that no drug administration will be given at Week 12 visit as part of the present study.	-Section 1.3, Schedule of Events, check was removed at Week 12 at the line "Study product administration at study center" and the corresponding footnotes were revised accordingly.
	-To clarify the moment when some assessments are to be taken during the visits.	-Schedule of event, footnotes #7, #8 and 15, clarification was added with regards to the moment these assessments are to be performed, prior to the study drug administration.

	-To detail how subjects who start to use prohibited medications for AD during the study will be handled.	-Synopsis, Schedule of event (footnote), Sections 5.3.1, 6.4.2, 8.3.1 and 8.3.2, to specify how subjects who start medication for AD during the study are handled and if study product discontinuation is required or not. Specifications with regards to how to handle missing data in the statistical analysis have been made in the statistical sections.
	-To remove the exclusion of certain body parts for the BSA calculation.	-Section 7.1.4, the following "([excluding palms, back of the hands, soles, scalp, genitals, and folds])" was removed as it was included in the protocol in error.
	-To correct typographical errors.	-Synopsis, secondary pharmacokinetic endpoint revised to be consistent with section 3. -Section 5.2, criterion # 16, bullet numbering corrected to be consistent with the numbering in the synopsis. -Section 5.2, criterion # 37 (in version 1.0), revised to be consistent with criterion in the synopsis. -Section 9.10, section title was corrected. -Minor typographical errors corrected throughout the document.
3.0 / 07 February 2019	- To revise the inclusion criterion related to body mass index (BMI) in order to allow wider pool of subjects access to the trial.	- Synopsis and Section 5.1, inclusion criterion #7, BMI was revised to $\leq$ 38 kg/m^2.

STATEMENT OF COMPLIANCE

The trial will be conducted in accordance with the protocol, International Council for Harmonisation (ICH) Good Clinical Practice (GCP), the Declaration of Helsinki, and applicable local regulations. The principal investigator will assure that no planned deviation from, or changes to the protocol will take place without prior agreement from the sponsor and documented approval from the institutional review board (IRB) / ethic committee (EC), except where necessary to eliminate an immediate hazard(s) to the trial subjects. All personnel involved in the conduct of this study have completed ICH GCP training.

The protocol, informed consent form(s), recruitment materials, and all subject materials will be submitted to the IRB/EC for review and approval. Approval of both the protocol and the consent form must be obtained before any subject is enrolled. Any amendment to the protocol will require review and approval by the IRB/EC before the changes are implemented to the study. All changes to the consent form will be IRB/EC approved.

SIGNATURE PAGE

The signatures below constitute the approval of this protocol and provide the necessary assurances that this trial will be conducted according to this protocol, local legal and regulatory requirements, the Declaration of Helsinki, and ICH GCP guidelines.

Sponsor:

Niranjan Rao, PhD
Vice President, Clinical Development
Asana BioSciences, LLC

Feb 7, 2019
Date (DD-MMM-YYYY)

Louis Denis, MD
Chief Medical Officer
Asana BioSciences, LLC

07-FEB-2019
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Scientific Affairs:

Julie Massicotte, BSc
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12-Feb-2019
Date (DD-MMM-YYYY)

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Diane Potvin, MSc
Director, Biostatistics
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12-Feb-2019
Date (DD-MMM-YYYY)

PRINCIPAL/QUALIFIED INVESTIGATOR SIGNATURE PAGE

Investigator Name: _____

Signature: _____ **Date:** _____
(DD-MMM-YYYY)

Institution Name: _____

By my signature, I agree to personally supervise the conduct of this study at my study site and to ensure its conduct is in compliance with the protocol, informed consent, institutional review board/independent ethics committee procedures, instructions from sponsor's representatives, the Declaration of Helsinki, ICH GCP guidelines, applicable Canadian regulations, applicable European regulations, applicable United States federal regulations, and local regulations governing the conduct of clinical studies.

LIST OF ABBREVIATIONS

AD	atopic dermatitis
AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
anti-HBc	antibody to hepatitis B core antigen
AST	aspartate aminotransferase
β-hCG	β-human chorionic gonadotropin
BMI	body mass index
BSA	body surface area
BUN	blood urea nitrogen
CK	creatine kinase
CMH	Cochran Mantel Hansel
CONSORT	Consolidated Standards of Reporting Trials
CRF	case report form
CRP	C-reactive protein
CPK	creatine phosphokinase
CRO	contract research organization
CV	coefficient of variation
DSMB	Data and Safety Monitoring Board
DLQI	Dermatology Life Quality Index
EASI	Eczema Area and Severity Index
EC	ethic committee
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
ET	early termination
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GERD	Gastroesophageal reflux disease
GGT	gamma-glutamyl-transferase
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCT	hematocrit
HCV	hepatitis C virus
HDL	high-density lipoproteins
Hgb	hemoglobin
HIV	human immunodeficiency virus
IB	investigator brochure
ICH	International Council for Harmonisation
IGA	Investigator Global Assessment
IRB	institutional review board
ITT	intent-to-treat (population)

IWRS	Interactive Web Response System
LDH	lactate dehydrogenase
LDL	low-density lipoproteins
LMW	low molecular weight
JAK	janus kinase
Mapi	Mapi Life Sciences
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Model Repeated Measures
MPV	mean platelet volume
NRS	numeric rating scale
NSAID	nonsteroidal anti-inflammatory drug
NYHA	New York Heart Association
OLE	open label extension study
PD	pharmacodynamic
PK	pharmacokinetic
PLT	platelets
POEM	Patient-Oriented Eczema Measure
PP	per-protocol (population)
PPD	purified protein derivative
PUVA	psoralen-UV-A
QC	quality control
RBC	red blood cell (count)
RNA	ribonucleic acid
SAE	serious adverse event
SAF	safety (population)
SAP	statistical analysis plan
SCORAD	SCORing Atopic Dermatitis
SD	standard deviation
SYK	spleen tyrosine kinase
TB	tuberculosis
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
UV	ultraviolet
VTE	venous thromboembolic event
WBC	white blood cell (count)
WHO	World Health Organization
WOCBP	women of childbearing potential

1 PROTOCOL SUMMARY

1.1 Synopsis

Name of Sponsor/Company: Asana BioSciences, LLC	**Name of Investigational Product:** ASN002	**Name of Active Ingredient:** ASN002

Title of Study:

A Randomized, Double-Blind, Placebo-Controlled, Phase 2b Study to Evaluate the Efficacy, Safety, Tolerability, and Pharmacokinetics of ASN002 in Subjects with Moderate to Severe Atopic Dermatitis

Phase of Development:

Phase 2b

Study Center(s):

Approximately 50 study centers located in the United States, Canada, and Germany will participate in this study.

Number of Subjects (planned):

Approximately 220 subjects will be included in this study to reach 160 evaluable subjects.

Duration of Study:

The maximum study duration per subject is up to 20 weeks (including up to 4 weeks for the screening period, up to 12 weeks for the treatment period, and up to 4 weeks for the follow-up period).

Investigational Product, Dosage, and Mode of Administration:

ASN002 40, 60, or 80 mg or placebo orally administered once daily for 12 weeks. ASN002 will be available in 20-mg strength tablets.

Subjects will be randomized in a 1:1:1:1 ratio. Randomization will be stratified by baseline disease severity ([Eczema Area and Severity Index (EASI) = 16.0-21.2] vs. [EASI =21.3-29.9] vs. [EASI = ≥ 30.0]) and biopsy collection.

Objectives:

Primary:

- To evaluate the efficacy of ASN002 in subjects with moderate to severe atopic dermatitis (AD)

Secondary:

- To evaluate the safety and tolerability of ASN002 in subjects with moderate to severe AD
- To evaluate the pharmacokinetic (PK) profile of ASN002 in subjects with moderate to severe AD

Exploratory:

- To assess population PK of ASN002 in AD subjects via a population PK analysis approach
- To evaluate pharmacodynamic (PD) and biomarkers for evidence of drug activity in subjects with moderate to severe AD

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- To explore the relationships between PK exposure and clinical measurement (e.g., biomarker, efficacy, and safety) as appropriate

Endpoints:

Primary Endpoint:

- Change from baseline in EASI score at Week 12

Secondary Endpoints:

Secondary efficacy endpoints include:

- Change from baseline in EASI score at Weeks 2, 4, and 8
- Percent change from baseline in EASI score at Weeks 2, 4, 8, and 12
- Proportion of subjects with at least a 50% reduction from baseline in EASI (EASI50) at Weeks 2, 4, 8, and 12
- Proportion of subjects achieving at least a 75% reduction from baseline in EASI (EASI75) at Weeks 2, 4, 8, and 12
- Proportion of subjects achieving at least a 90% reduction from baseline in EASI (EASI90) at Weeks 2, 4, 8, and 12
- Time to achieve EASI50, EASI75, and EASI90 relative to baseline.
- Proportion of subjects achieving at least a 2-grade reduction from baseline to clear (0) or almost clear (1) in Investigator's Global Assessment (IGA) at Weeks 2, 4, 8, and 12
- Proportion of subjects achieving at least a 2-grade reduction from baseline in IGA at Weeks 2, 4, 8, and 12
- Proportion of subjects achieving an IGA of clear (0) or almost clear (1) at Weeks 2, 4, 8, and 12
- Change from baseline in SCORing Atopic Dermatitis (SCORAD) at Weeks 2, 4, 8, and 12
- Change from baseline in 5-D Pruritus Scale at Weeks 2, 4, 8, and 12
- Change and percent change from baseline in single daily timepoint pruritus Numeric Rating Scale (NRS) at Week 1
- Change and percent change from baseline in weekly average of the peak daily pruritus NRS at Weeks 1, 2, 4, 8, and 12
- Proportion of subjects achieving at least a 4-point reduction from baseline in weekly average of the peak daily pruritus NRS at Weeks 1, 2, 4, 8, and 12
- Change and percent change from baseline in Body Surface Area (BSA) involved with AD at Weeks 2, 4, 8, and 12
- Change from baseline in Patient-Oriented Eczema Measure (POEM) at Weeks 2, 4, 8, and 12
- Change from baseline in Dermatology Life Quality Index (DLQI) at Weeks 2, 4, 8, and 12

Secondary safety endpoints include:

- Number of treatment-emergent adverse events (TEAEs)
- Number of drug-related TEAEs
- Proportion of subjects withdrawing from worsening AD at Weeks 2, 4, 8, and 12

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- Changes in vital signs, physical examinations, electrocardiogram (ECG), and safety laboratory tests

Secondary pharmacokinetic endpoint includes:

- Measurement of plasma concentrations of ASN002 in all subjects receiving ASN002 treatment

Exploratory Endpoints:

Exploratory endpoints include:

- Change from baseline in expression levels and kinase activity of key disease pathways in skin biopsies, such as Th2 and other T helper cell axes
- Changes from baseline in cellular infiltrates of T-cells and dendritic cells
- Changes from baseline in epidermal hyperplasia measures (epidermal thickness, ki67, and K16 expression)
- Changes from baseline in mRNA and protein expression of differentiation markers
- Changes in inflammatory measures in peripheral blood using proteomics
- Characterization of population PK parameters via nonlinear mixed-effects modeling
- Changes from baseline in clinical safety, efficacy, and biomarker measurements in relationship to PK exposure

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Study Design:

Approximately 220 subjects with moderate to severe AD (as defined by a BSA involved with AD of ≥ 10%, an EASI ≥ 16, and an IGA ≥ 3 at Day 1) will be included in this randomized, double-blind, placebo-controlled, multicenter, Phase 2b study.

All subjects will sign an informed consent and undergo screening for study eligibility. After a screening period of no more than 30 days (from Day -30 to Day -1), eligible subjects will be randomized (1:1:1:1) on Day 1 to receive ASN002 at 40 mg, 60 mg, or 80 mg, or placebo once daily for 12 weeks, followed by a 4-week follow up period for subjects not participating in the open label extension (OLE) study. For scheduled study visits, subjects will come to the study centers on seven occasions: screening; Day 1; Weeks 2, 4, 8, and 12; and Week 16/early termination (ET) for subjects not participating in the OLE study.

Efficacy will be assessed using IGA, EASI, SCORAD, BSA, pruritus NRS (daily), and 5-D pruritus scale. Quality of life will be evaluated using POEM and DLQI.

Safety will be assessed by adverse events (AEs), physical examination, vital signs, 12-lead ECG, and clinical laboratory tests.

Pre- and post-dose PK blood samples will be collected from all subjects on a sparse sampling schedule on Day 1 and Weeks 2, 4, 8 and 12 (or ET visit, if applicable).

At selected study centers, in a subset of approximately 68 subjects who consent, PD blood samples will be collected pre-dose on Day 1 and Week 12 (or ET visit, if applicable). PD samples will be obtained from the same subjects who consent to biopsy collection. An additional PD blood sample will be collected at Week 4 in subjects who also consent to four skin biopsies.

At selected study centers, in a subset of approximately 68 subjects who consent, three or four skin biopsies will be collected during this study. Two 4.5-mm punch biopsies (one from lesional skin and one from adjacent nonlesional skin) will be collected at Day 1, and one 4.5-mm punch biopsy will be collected from the same lesional skin (outside the scar of the previous biopsy, at least 1 cm away from the previous scar) at Week 12 (or ET visit, if applicable). In addition, one 4.5-mm punch biopsy will be collected from the same lesional skin (outside the scar of the previous biopsy, at least 1 cm away from the previous scar) at Week 4 in subjects who consent to four skin biopsies.

At selected study centers, in a subset of approximately 68 subjects who consent, medical photographs of the area of worst AD involvement will be taken to illustrate any visible clinical change.

Inclusion/Exclusion Criteria:

Inclusion criteria:

1. Male or female subject, aged 18 to 75 years, inclusive, at the time of consent.
2. Subject has clinically confirmed diagnosis of active atopic dermatitis, according to Hanifin and Rajka criteria.
3. Subject has at least a 6-month history of atopic dermatitis and had no significant flares in atopic dermatitis for at least 4 weeks before screening (information obtained from medical chart or subject's physician, or directly from the subject).
4. Subject has an EASI score ≥ 16 at Day 1.

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5. Subject has moderate to severe atopic dermatitis at Day 1, as defined by an IGA ≥ 3.
6. Subject has atopic dermatitis covering ≥ 10% of the BSA on Day 1.
7. Subject has a body mass index (BMI) ≤ 38 kg/m^2.
8. Subject has a history of inadequate response to topical corticosteroids or calcineurin inhibitors as treatment for AD within 1 year before the screening visit (information obtained from medical chart or subject history).
9. Subject has been using an emollient (except those containing urea) either once daily or twice daily for at least 1 week prior to Day 1 and agrees to continue using that same emollient, daily and at the same frequency, throughout the study. Note: On the day of scheduled visits, subjects cannot apply emollient before their scheduled visit time.
10. For women of childbearing potential involved in any sexual intercourse that could lead to pregnancy: the subject must agree to use a highly effective contraceptive method from at least 4 weeks before Day 1 until at least 4 weeks after the last study product administration. Highly effective contraceptive methods include hormonal contraceptives (combined oral contraceptive, patch, vaginal ring, injectable, or implant), intrauterine devices or intrauterine systems, vasectomized partner(s), tubal ligation, or double barrier methods of contraception (barrier methods include male condom, female condom, cervical cap, diaphragm, contraceptive sponge) in conjunction with spermicide.
    Note: Subjects must have been on a stable dose of hormonal contraceptives for at least 4 weeks before Day 1.

    Note: The above list of contraceptive methods does not apply to subjects who are abstinent for at least 4 weeks before Day 1 and will continue to be abstinent from penile-vaginal intercourse throughout the study. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the participant.
    Note: For countries where double barrier methods are not accepted as highly effective contraception, then this option must not be considered.
    Note: A woman of nonchildbearing potential is as follows:
    a. Woman who has had surgical sterilization (hysterectomy, bilateral oophorectomy, or bilateral salpingectomy);
    b. Woman who has had a cessation of menses for at least 12 months without an alternative medical cause, and a follicle-stimulating hormone (FSH) test confirming nonchildbearing potential (refer to laboratory reference ranges for confirmatory levels).
11. For men involved in any sexual intercourse that could lead to pregnancy, subject must agree to use one of the highly effective contraceptive methods listed in Inclusion Criterion #10, from Day 1 until at least 4 weeks after the last study product administration. If the female partner of a male subject use any of the hormonal contraceptives method listed above, this contraceptive method must be used by the female partner from at least 4 weeks before Day 1 until at least 4 weeks after the last study product administration.
12. Female of childbearing potential has had a negative serum pregnancy test at screening and negative urine pregnancy test on Day 1.
13. Subject is willing to participate and is capable of giving informed consent. Note: Consent must be obtained prior to any study-related procedures.
14. Subjects must be willing to comply with all study procedures and must be available for the duration of the study.

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Exclusion criteria:

1. Subject is a female who is breastfeeding, pregnant, or who is planning to become pregnant during the study.
2. Subject has clinically infected atopic dermatitis.
3. Subject has a history of skin disease or presence of skin condition that, in the opinion of the investigator, would interfere with the study assessments.
4. Active infection, including skin infection, requiring treatment.
5. Subject has a history of cancer or lymphoproliferative disease within 5 years prior to Day 1. Subjects with successfully treated nonmetastatic cutaneous squamous cell or basal cell carcinoma and/or localized carcinoma in situ of the cervix are not to be excluded.
6. Subject has any clinically significant medical condition or physical/laboratory/ECG/vital signs abnormality that would, in the opinion of the investigator, put the subject at undue risk or interfere with interpretation of study results.
7. Subject has 12-lead ECG abnormalities considered by the investigator to be clinically significant or QTc F $\geq$ 450 milliseconds, regardless of clinical significance, at screening. Abnormal ECG may be confirmed with one repeat assessment. For subjects with QTcF$\geq$450 msec on initial ECG, the mean of the two QTc F assessments will determine eligibility.
8. Subject has a history of congestive heart failure New York Heart Association (NYHA) class III or IV.
9. Subject has a history of erythrodermic, refractory or unstable skin disease, including AD, that requires frequent hospitalizations and/or frequent intravenous treatment for skin infections over the last year
10. Subject has a history of eczema herpeticum within 12 months, and/or a history of 2 or more episodes of eczema herpeticum in the past.
11. Subject has a history of recurrent venous thromboembolic event (VTE) (>=2)
12. Subject has experienced any of the following within the last 6 months prior to Day 1: VTE myocardial infarction, angioplasty, or cardiac stent placement, unstable ischemic heart disease, or stroke.
13. Subject had other major surgery within 8 weeks prior to Day 1 or has a major surgery planned during the study.
14. Subject is known to have immune deficiency or is immunocompromised.
15. Subject has positive results for hepatitis B surface antigens (HBsAg), antibodies to hepatitis B core antigens (anti-HBc), hepatitis C virus (HCV), or human immunodeficiency virus (HIV) at the screening visit.
16. Presence of any of the following laboratory abnormalities at the screening visit:
    a. Hemoglobin < 11 g/dL;
    b. White blood cell (WBC) < 3.0 x 10^3 /µL;
    c. Platelet count < 125 x 10^3 /µL;
    d. Neutrophils < 1.8 x 10^3 /µL;
    e. Lymphocytes < 1.0 x 10^3 /µL;
    f. Aspartate aminotransferase (AST)/alanine aminotransferase (ALT) > 2 x the upper

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limit of normal (ULN);

g. Total bilirubin > 1.2 x ULN (except for elevated indirect bilirubin secondary to Gilbert's syndrome);

h. Creatinine > ULN.

17. Subjects has uncontrolled hypertension within the last 1 month prior to screening or blood pressure at screening of systolic blood pressure >160 mm Hg or diastolic BP >95 mm Hg, confirmed by one repeat assessment.
18. Subject has a known active tuberculosis or a positive tuberculosis (TB) infection test. Subject will be evaluated for latent TB infection with a purified protein derivative (PPD) test or a QuantiFERON-TB Gold test. Subjects who demonstrate evidence of latent TB infection (either PPD ≥5 mm of induration or positive QuantiFERON-TB Gold test, irrespective of bacille Calmette-Guérin vaccination status) will only be allowed to participate in the study if there is documented evidence of a completed adequate treatment course for latent TB (with negative chest x-ray findings for active TB).
19. Subject has difficulty swallowing medications, or known history of malabsorption syndrome.
20. Subject has a history of recurrent gastroesophageal reflux disease (GERD) requiring the use of proton pump inhibitors within the last month.
21. Subject has a known history of diverticulitis.
22. Subject has uncontrolled diabetes.
23. Any medical or psychiatric condition which, in the opinion of the investigator or the sponsor's medical monitor, would place the subject at risk, interfere with participation in the study, or interfere with the interpretation of study results.
24. Subject has used dupilumab within 12 weeks prior to Day 1.
25. Subject has received any UV-B phototherapy (including tanning beds) or excimer laser within 4 weeks prior to Day 1.
26. Subject has had psoralen-UV-A (PUVA) treatment within 4 weeks prior to Day 1.
27. Subject has used doxepin within 1 week prior to Day 1.
28. Subject has used hydroxyzine or diphenhydramine within 1 week prior to Day 1.
29. Subject has used topical products containing urea within 1 week prior to Day 1.
30. Subject has used systemic antibiotics within 2 weeks or topical antibiotics within 1 week prior to Day 1.
31. Subject has used any topical medicated treatment for atopic dermatitis within 2 weeks prior to Day 1, including, but not limited to, topical corticosteroids, crisaborole and any other topical phosphodiesterase-4 inhibitor, calcineurin inhibitors, tars, bleach, antimicrobials, medical devices, and bleach baths.
32. Subject has used systemic treatments (other than biologics) that could affect atopic dermatitis less than 4 weeks prior to Day 1 (e.g., retinoids, calcineurin inhibitors, methotrexate, cyclosporine, hydroxycarbamide [hydroxyurea], azathioprine, oral/injectable corticosteroids). Note: Intranasal corticosteroids, eye drops containing corticosteroids, and inhaled corticosteroids for stable medical conditions are allowed.
33. Subject has received any marketed or investigational biological agent within 12 weeks or 5 half-lives (whichever is longer) prior to Day 1.

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34. Subject is currently receiving any other medication for AD.
35. Subject is currently receiving a nonbiological investigational product or device or has received one within 4 weeks prior to Day 1.
36. Subject has excessive sun exposure, is planning a trip to a sunny climate, or has used tanning booths within 4 weeks prior to Day 1, or is not willing to minimize natural and artificial sunlight exposure during the study. Use of sunscreen products and protective apparel are recommended when exposure cannot be avoided.
37. Subject has received a live attenuated vaccine within 4 weeks prior to Day 1 or plans to receive a live attenuated vaccine during the study and up to 4 weeks or 5 half-lives (of the study product), whichever is longer, after the last study product administration.
38. Subject has used ASN002.
39. Subject had prior treatment with a systemic SYK or JAK inhibitor for which the subject received no clinical benefit in the opinion of the investigator, or the subject relapsed whilst on therapy, or was withdrawn for safety reasons.
40. Subject has a known hypersensitivity to ASN002 or its excipients.
41. Subject has a known history of clinically significant drug or alcohol abuse in the last year prior to Day 1.
42. Subject has a close affiliation with the investigator (e.g., a close relative) including any study staff of the sites or persons working at the CRO, or subject is an employee of the sponsor.
43. Subject is institutionalized because of legal or regulatory order.
44. Only for subjects consenting to biopsies:
    a. Subject has a history of an allergic reaction or significant sensitivity to lidocaine or other local anesthetics;
    b. Subject has a history of hypertrophic scarring or keloid formation in scars or suture sites;
    c. Subject is taking anticoagulant medication, such as heparin, low molecular weight (LMW)-heparin, warfarin, antiplatelets (except low-dose aspirin which will be allowed), within 2 weeks prior to Day 1, or has a contraindication to skin biopsies. Nonsteroidal anti-inflammatory drugs [NSAIDs] will not be considered antiplatelets and will be allowed.

Statistical methods:

Continuous variables will be summarized in tables and will include the number of subjects, mean, standard deviation (SD), percent of coefficient of variance (CV%), median, minimum, and maximum. Categorical variables will be presented in tables as frequencies and percentages. A statistical analysis plan (SAP) will provide additional details on the approach to the analysis and data displays.

Efficacy Analyses:

The primary efficacy endpoint will be analyzed using a repeated measures analysis of covariance on change-from-baseline variable to compare the time profile between treatments where the visit will be the time factor; and the stratification factors, treatment group, and interaction term for treatment-by-visit will be the fixed effects and the baseline value will be the covariate. An unstructured variance-covariance matrix will be used.

For categorical efficacy endpoints involving proportions of IGA, EASI and NRS (e.g. the proportion of subjects achieving at least a 2-grade reduction from baseline to clear (0) or almost clear (1) in IGA at

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week 12), a Cochran Mantel Hansel test (CMH) controlling for the stratification variables will be performed.

For the primary endpoint of change-from-baseline in EASI at Week 12, a Bonferroni adjustment will be done to test the three comparisons of interest (40 mg vs. Placebo, 60 mg vs. Placebo and 80 mg vs. Placebo) at nominal alpha of 0.0167.

Safety Analyses:

The safety analysis will include reported AEs and other safety information (i.e., clinical laboratory evaluations, vital signs, physical examination, and 12-lead ECG results). A summary of safety results will be presented for each treatment group.

PK Analyses:

ASN002 concentration data will be summarized based on nominal timepoints using descriptive statistics, such as mean, SD, CV%, median, minimum and maximum.

Population PK analysis will be performed using nonlinear mixed-effects modeling approach with first-order conditional methods. This analysis may be combined with PK concentrations from other clinical trials in healthy and AD subjects as appropriate.

PD Analyses:

Biomarker levels will be compared to placebo adjusted change from baseline over time for each treatment group, and the parameters will be summarized by treatment group and overall using descriptive statistics.

PK/PD Analyses:

PK-efficacy, PK-safety and PK-biomarkers relationships will be explored using linear regression, loess plots, Hills functions, or logistic regression, as appropriate.

Sample Size Consideration:

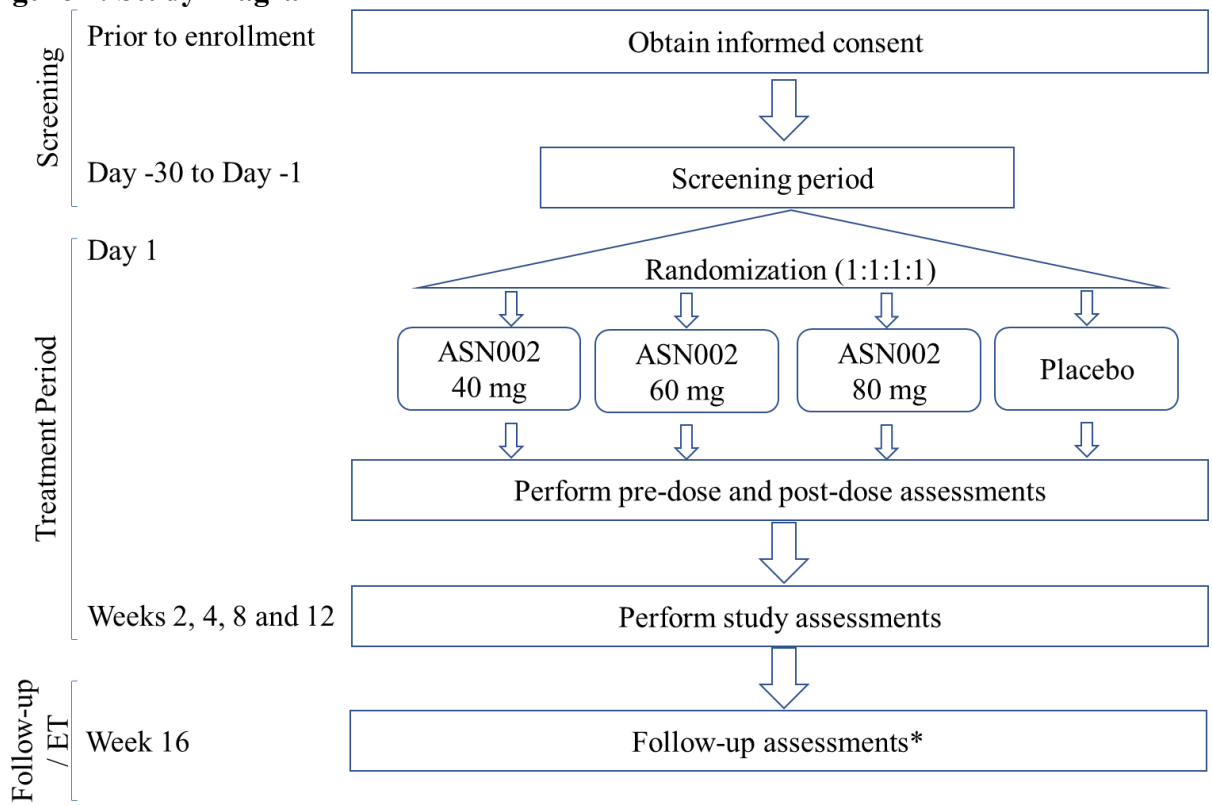
Using the following assumptions: a change-from-baseline in EASI at week 12 of at least -15 in the ASN002 dosing groups, a change-from-baseline of -8 in the placebo group, a common standard-deviation of 8, alpha of 0.0167 for each comparison of interest, we would need 40 subjects per group in order to achieve a power of 92% on the primary efficacy endpoint.

Moreover, with 46 subjects per group, we would have 80% power to show a statistically significant difference between the higher dosing group and placebo in IGA responses (one of the key secondary efficacy endpoint), assuming a response of 37.5% vs. 11.1% in the higher dosing and placebo groups, respectively, using an alpha of 5%.

Thus, assuming about 15% dropout rate, 55 subjects per group will need to be enrolled in this trial for a total of 220 subjects in order to have a minimum of 46 subjects per group to evaluate efficacy with adequate power.

1.2 Study Diagram

Figure 1: Study Diagram



*The follow-up assessments at Week 16 will be for subjects who completed the study and declined to participate in the OLE study.

1.3 Schedule of Events

The screening evaluation will only be performed after the subject has agreed to participate and has signed and dated the informed consent form. No treatment or trial-related procedures will be initiated before the informed consent is signed. The Day 1 visit must be performed, at the latest, 30 days after the screening visit. The screening evaluation will be performed according to the inclusion and exclusion criteria. If the subject fulfills all inclusion criteria and no exclusion criteria, he or she may be included in the study.

Table 1 provides a description of the procedures to be performed at each visit.

If assessments are scheduled at the same time, then the assessments should occur in the following order:

- Vital signs (within 1 hour of dosing)
- 12-lead ECG
- Blood draws for PK and PD samples (time window vs drug administration detailed in footer of Table 1)

Note: The timing of the assessments should allow the blood draw to occur within the allowed window of the nominal time.

Table 1: Schedule of Events

Study Visits	Screening	Treatment Period					Follow-up / ET[12]
		Day 1	Week 2	Week 4	Week 8	Week 12	Week 16
Window (days)	-30 to -1		±1	±2	±2	±2	±2
Informed consent	X						
Demographics	X						
Medical and surgical history	X	X					
Inclusion-exclusion criteria	X	X					
Pregnancy test[1]	X	X	X	X	X	X	X
Physical examination	X	X		X[3]		X	X[3]
Vital signs[2]	X	X	X	X	X	X	X
ECG[5]	X	X		X		X	X[4]
Clinical laboratory tests (hematology, chemistry, and urinalysis)	X	X		X		X	X
Serology (HIV, HBV, HCV)	X						
Tuberculosis evaluation[6]	X						
BSA	X	X	X	X	X	X	X
IGA	X	X	X	X	X	X	X
EASI	X	X	X	X	X	X	X
SCORAD		X	X	X	X	X	X
Pruritus NRS		X	X	X	X	X	X
5-D pruritus scale		X	X	X	X	X	X
DLQI		X	X	X	X	X	X
POEM		X	X	X	X	X	X
Skin biopsies collection[7]		X		X[9]		X	X[4]
Blood sampling for PD analyses[8]		X		X[9]		X	X[4]
Blood sampling for PK evaluation		X[10]	X[11]	X[10]	X[11]	X[11]	X[4,11]
Randomization		X					
Study product administration at study center		X	X	X	X		
Study product administration daily[13]		X----------	----------	----------	----------	----------X	
Emollient use		X----------	----------	----------	----------	----------	----------X
Daily subject diary[14]		X ----------	----------	----------	----------	----------	----------X
Dispensing of study product		X		X	X		
Collecting of study product				X	X	X	X[4]
Study product accountability/ compliance			X	X	X	X	X[4]

Study Visits	Screening	Treatment Period					Follow-up / ET[12]
		Day 1	Week 2	Week 4	Week 8	Week 12	Week 16
Window (days)	-30 to -1		±1	±2	±2	±2	±2
Verification of subject diary		X	X	X	X	X	X
Photograph AD area[15]		X		X		X	X
Concomitant medication	X	X	X	X	X	X	X
Adverse events evaluation	X	X	X	X	X	X	X

BSA=body surface area; DLQI=Dermatology Life Quality Index; EASI=Eczema Area and Severity Index; ECG=electrocardiogram; ET=early termination; HBV=hepatitis B virus; HCV=hepatitis C virus; HIV=human immunodeficiency virus; IGA=Investigator Global Assessment; NRS=numeric rating scale; PD=pharmacodynamic; PK=pharmacokinetics; POEM=Patient-Oriented Eczema Measure; SCORAD=SCORing Atopic Dermatitis.

[1] Females of childbearing potential only. Serum pregnancy test at screening and urine pregnancy test at other visits.

[2] Including height, weight and BMI. Height will be measured only at screening and the same value will be used for BMI calculation at other visits.

[3] Brief physical examinations.

[4] Only at ET

[5] ECG will be recorded at 0 (pre-dose, within 1 hour of dosing), 1 (± 30 min), and 3 (± 1 hour) hours post-dose on Day 1 and Week 4. ECG will be recorded only once at screening, Week 12, and ET visits.

[6] If PPD is used, a second screening visit will be necessary.

[7]Optional, only for a subset of approximately 68 subjects who consent: two 4.5-mm skin biopsies at Day 1 (one from lesional skin and one from adjacent nonlesional skin) and one at Week 12/ET (from lesional skin). Subjects consenting to biopsies collection must also consent to PD samples. Biopsies should be collected prior to study product administration.

[8] Optional, only for a subset of approximately 68 subjects who consent: PD samples to be drawn as trough samples prior to study product administration. Subjects consenting to PD samples must also consent to biopsies collection. PD samples should be collected prior to study product administration.

[9] An additional skin biopsy from lesional skin and PD sample will be collected at Week 4 for subjects who consent to four biopsies.

[10] PK samples will be collected at 0 (pre-dose), 1 (± 30 min), 3 (± 30 min), and 6 (between 5 to 12 hours post-dose) hours post-dose. The dosing time for the previous day should be recorded accurately.

[11] PK samples will be collected at 0 (pre-dose) and 2 (± 30 min) hours post-dose. The dosing time for the previous day should be recorded accurately. At ET and Week 12, only one PK sample will be collected.

[12] Follow-up visit for subjects not participating in the OLE study. Subjects who have their study product discontinued due to the start of a prohibited medication for the treatment of AD or for any other safety reasons will be asked to come back for an additional follow-up visit about 4 weeks after the study product discontinuation (in addition to the ET visit). Refer to section 6.4.2 for more details.

[13] Study products will be taken at home daily for 12 weeks, except on study visit days when the study products will be administered on site. No drug administration will be given at Week 12 visit as part of the present study.

[14] Pruritus NRS, emollient use, time of study products administration, and fasting conditions will be recorded daily for 12 weeks in a subject diary. Pruritus NRS and emollient use will be recorded daily in a diary up to Week 16 visit for subjects not entering in the OLE study. Compliance to diary entry, including emollient use, will be verified by the site at every visit.

[15] Optional, only for a subset of approximately 68 subjects who consent. Photographs should be performed prior to drug administration and biopsy collection (for subjects consenting to biopsies).

2 INTRODUCTION

2.1 Background

2.1.1 Atopic Dermatitis

Atopic dermatitis (AD) is a chronic inflammatory skin disease. Inflammation, pruritus, papules, lichenification, excoriations, xerosis and oozing clinically characterize AD.(1) Onset typically occurs in children and can improve in adulthood, however, late onset can also occur.(2) Atopic dermatitis affects 10-20% of children and 1-3% of adults.(2, 3) Moreover, recent studies suggest that the prevalence of AD in adults could be much higher.(4) Prevalence has also been observed to be higher in industrialized countries, suggesting, at least partially, an environmental link.(5) The quality of life and psychological state of patients with AD, as well as the parents of patients can be greatly impacted by this disease.(6, 7) Pruritus prevalence in AD patients is greater than 80% and greatly impairs their quality of life by causing sleep and psychological disturbance.(8)

It is a heterogeneous disease with a wide spectrum of clinical phenotype and a complex pathophysiology.(9, 10) The precise etiology of AD remains unclear but is likely to be multifactorial in nature, involving genetics, abnormalities in the skin barrier, immune system defects, and environmental triggers (e.g., allergens, irritants, microbes, diet, stress, air quality).(3, 11)

In recent years, the understanding of the clinical characterization of AD phenotypes and molecular mechanisms of the disease has advanced greatly giving hope for the development of new therapeutic agents.(5, 10, 12, 13) Janus kinase (JAK) and Spleen tyrosine kinase (SYK) are tyrosine kinases that have been shown to be implicated in the pathogenesis of various types of autoimmune and inflammatory diseases.(14, 15) It is understood that AD is primarily a T cell-driven disease.(16) Atopic dermatitis was shown to have a strong Th2 response where IL-4 promotes the differentiation of Th2 cells, which are regulated by the JAK signaling pathway. Moreover, activation of SYK leads to the release of various inflammatory mediators and plays a role in downstream signaling involved in the pathology of several allergic and autoimmune diseases.(14, 17) Therefore, targeting both JAK and SYK kinases may provide a new therapeutic approach in the treatment of inflammatory disorders, such as atopic dermatitis.

2.1.2 ASN002 in Atopic Dermatitis

ASN002 is an orally bioavailable, potent dual inhibitor of JAK and SYK kinases with 50% inhibitory concentrations (IC50 values) of 5-46 nM in biochemical assays. In cell-based mechanistic assays, the compound showed inhibition of IgE-immune complex induced degranulation and phosphorylation of LAT (Linker for Activation of T cells) a substrate of SYK, and also IL-6 induced phosphorylation of STAT3 (IC50 range 14–143 nM). In a collagen-induced arthritis model, ASN002 demonstrated a significant reduction in arthritic, histopathology and radiographic scores when compared to vehicle. The compound also showed broad antiproliferative activity in a panel of cell lines representing both solid and leukemia/lymphoma tumor types. The data from both in vitro (cell line) and in vivo efficacy

studies with ASN002 provide strong rationale for its evaluation in subjects with atopic dermatitis. In a Phase 1b study (ASN002AD-101), plasma concentrations of ASN002 were measured in subjects with atopic dermatitis following single and repeated once daily oral administration at 20, 40 and 80 mg. At steady state, C_{max} and AUC were dose dependent with approximately 1.5-fold or less accumulation compared to those on Day 1, and the mean elimination $t_{1/2}$ were 7.3-13.7 hours. At 80 mg, the mean C_{max} and AUC_{tau} of ASN002 at steady state were 252 ng/ml and 3340 ng*hr/ml, respectively. The safety and tolerability profile of ASN002 at all dose levels was excellent. The most common adverse event (AE) observed was transient, mild headache, mostly restricted to Day 1 likely due to fasting. There were no clinically significant laboratory changes including hematological parameters observed in this study. ASN002 showed robust clinical efficacy with nearly all patients obtaining a 50% improvement in disease severity (EASI50) at 40 mg and 80 mg once daily and substantial decreases in patient-reported itch measured by Numeric Rating Scale (NRS) after 4 weeks of treatment.

2.1.3 Study Rationale

In the previous clinical trial (ASN002AD-101), ASN002 has showed significant benefit for the treatment of atopic dermatitis, especially at 40 and 80 mg once-daily dosing regimens. This trial is to further investigate the benefit and risk of ASN002 in subjects with atopic dermatitis for a 12-week treatment duration.

Current therapies for AD provide relief of symptoms for most but not all patients. Additionally, they do not prevent or eradicate the disease. The development of medications that precisely target the molecular mediators of inflammation involved in AD is certainly a promising approach to treat this disease. There is definitely a need for new treatments in AD in order to increase the existing options available to clinicians.

The primary objective of this study is to assess the efficacy of ASN002 in subjects with moderate-to-severe atopic dermatitis. Safety and tolerability of ASN002 will also be evaluated as secondary endpoint as well as its pharmacokinetic profile. The doses to be administered in this study range between 40 and 80 mg, which were found to be well tolerated and safe in a previous Phase I study. Adverse events (AEs) observed in the Phase I study were of mild or moderate intensity following 80 mg dose. One SAE was reported (anxiety attack), which was not related to the study drug, and one event led to treatment discontinuation for one subject (hypertension) in the 80-mg cohort (refer to section 2.2.1 for more details). Once daily administration was chosen based on the data from the clinical studies in oncology subjects and healthy volunteers. Pharmacokinetic analyses indicate sufficient systemic exposure for ASN002 efficacy and a half-life of ~10 hours is adequate for maintaining target trough concentrations.

2.2 Risk/Benefit Assessment

2.2.1 Known Potential Risks

The data from both nonclinical and clinical studies with ASN002 suggest that it is safe and well-tolerated at the doses to be administered in the present study.

In cancer subjects, ASN002 has been well tolerated. The most common reported AEs were anemia, fatigue, chills, dizziness and diarrhea, as expected in heavily pretreated and refractory cancer patients.

The safety of ASN002 have also been studied in a safety, tolerability, PK and food effect study in healthy subjects at doses up to 100 mg following a single oral administration. The most common adverse event in this study was headache. One SAE, premature ventricular contractions, which were asymptomatic and mild, was experienced by one subject dosed with 50 mg ASN002 once. These resolved over 5 days without sequelae. This event was considered possibly related to study medication and unexpected.

The safety of ASN002 was also assessed in a previous Phase I study in AD patients. Adverse events (AEs) observed in the Phase I study were mild or moderate at doses up to 80 mg. There were no drug-related SAEs reported in this study. One SAE was reported (anxiety attack), which was not related to the study drug. In addition, one event led to treatment discontinuation for one subject (hypertension) in the 80-mg cohort. The corresponding patient was also on Ritalin and was observed with fluctuating blood pressure measurement results even after clearance of the study drug suggesting Stage 1 hypertension levels. It is also important to note that the patient also had borderline high level of blood pressure at baseline. Considering the above, this study suggests that ASN002 is safe and well-tolerated at doses up to 80 mg.

Further information related to previous clinical studies is available in the Investigator Brochure.

2.2.2 Known Potential Benefits

It is anticipated that subjects will see an improvement in their atopic dermatitis condition as a result of participating in this study, if they are randomized to active investigational product. Participation in this study may help generate future benefit for larger groups of patients with atopic dermatitis.

2.2.3 Assessment of Risks and Benefits

All quality, pharmacology and toxicology data, and satisfactory safety and tolerability data demonstrated in nonclinical and previous clinical studies are considered sufficient to expect a positive benefit/risk ratio for the treatment of atopic dermatitis with ASN002, and therefore to initiate this study.

The risk to subjects in this trial will be minimized by compliance with the eligibility criteria, proper study design, and close monitoring.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS
Primary	
To evaluate the efficacy of ASN002 in subjects with moderate to severe AD	Primary efficacy endpoint:
	• Change from baseline in EASI score at Week 12
	Secondary efficacy endpoints:
	• Change from baseline in EASI score at Weeks 2, 4, and 8 • Percent change from baseline in EASI score at Weeks 2, 4, 8, and 12 • Proportion of subjects with at least a 50% reduction from baseline in EASI (EASI50) at Weeks 2, 4, 8, and 12 • Proportion of subjects achieving at least a 75% reduction from baseline in EASI (EASI75) at Weeks 2, 4, 8, and 12 • Proportion of subjects achieving at least a 90% reduction from baseline in EASI (EASI90) at Weeks 2, 4, 8, and 12 • Time to achieve EASI50, EASI75, and EASI90 relative to baseline. • Proportion of subjects achieving at least a 2-grade reduction from baseline to clear (0) or almost clear (1) in IGA at Weeks 2, 4, 8, and 12 • Proportion of subjects achieving at least a 2-grade reduction from baseline in IGA at Weeks 2, 4, 8, and 12 • Proportion of subjects achieving an IGA of clear (0) or almost clear (1) at Weeks 2, 4, 8, and 12 • Change from baseline in SCORAD at Weeks 2, 4, 8, and 12 • Change from baseline in 5-D Pruritus Scale at Weeks 2, 4, 8, and 12 • Change and percent change from baseline in single daily timepoint pruritus NRS at Week 1 • Change and percent change from baseline in weekly average of the peak daily pruritus NRS at Weeks 1, 2, 4, 8, and 12 • Proportion of subjects achieving at least a 4-point reduction from baseline in weekly average of the peak daily pruritus NRS at Weeks 1, 2, 4, 8, and 12 • Change and percent change from baseline in BSA involved with AD at Weeks 2, 4, 8, and 12 • Change from baseline in POEM at Weeks 2, 4, 8, and 12 • Change from baseline in DLQI at Weeks 2, 4, 8, and 12
Secondary	
To evaluate the safety and tolerability of ASN002 in subjects with moderate to severe AD	Secondary safety endpoints:
	• Number of TEAEs

OBJECTIVES	ENDPOINTS
	• Number of drug-related TEAEs • Proportion of subjects withdrawing from worsening AD at Weeks 2, 4, 8, and 12 • Changes in vital signs, physical examinations, ECG, and safety laboratory tests
To evaluate the PK profile of ASN002 in subjects with moderate to severe AD	Secondary pharmacokinetic endpoint:
	• Measurement of plasma concentrations of ASN002 in all subjects receiving ASN002 treatment
Exploratory	
To assess population PK of ASN002 in AD subjects via a population PK analysis approach	• Characterization of population PK parameters via nonlinear mixed-effects modeling
To evaluate PD and biomarkers for evidence of drug activity in subjects with moderate to severe AD	• Change from baseline in expression levels and kinase activity of key disease pathways in skin biopsies, such as Th2 and other T helper cell axes • Changes from baseline in cellular infiltrates of T-cells and dendritic cells • Changes from baseline in epidermal hyperplasia measures (epidermal thickness, ki67, and K16 expression) • Changes from baseline in mRNA and protein expression of differentiation markers • Changes in inflammatory measures in peripheral blood using proteomics
To explore the relationships between PK exposure and clinical measurement (e.g., biomarker, efficacy, and safety) as appropriate	• Changes from baseline in clinical safety, efficacy and biomarker measurements in relationship to PK exposure

4 STUDY DESIGN

4.1 Overall Design

This study will be performed at approximately 50 study centers located in the United States, Canada and Germany.

This study is a randomized, double-blind, placebo-controlled, multicenter, Phase 2b study. Approximately 220 subjects with moderate to severe AD (as defined by a BSA involved with AD of ≥ 10%, an EASI ≥ 16, and an IGA ≥ 3 at Day 1) will be included in this study to complete the study with at least 160 evaluable subjects. Subjects will be men or women, aged 18 to 75 years, inclusive, at the time of consent.

Each subject should read and sign an informed consent form prior to any screening procedures being performed. Subjects who fulfill all of the inclusion criteria and none of the exclusion criteria will be accepted into the study. After a screening period of no more than 30 days (from Day -30 to Day -1), eligible subjects will be randomized (1:1:1:1) on Day 1 to receive ASN002 at 40 mg, 60 mg, or 80 mg, or placebo once daily for 12 weeks. The treatment period will be followed by a 4-week follow-up period for subjects not participating in the open label extension (OLE) study. For scheduled study visits, subjects will come to the study centers on seven occasions: screening, Day 1, Weeks 2, 4, 8, and 12, and Week 16/ ET for subjects not participating in the OLE study.

Efficacy will be assessed by IGA, EASI, SCORAD, BSA, pruritus NRS (daily), and 5-D pruritus scale. Quality of life will be evaluated using POEM and DLQI.

Safety will be assessed by AEs, physical examination, vital signs, 12-lead ECG, and clinical laboratory tests.

Pre- and post-dose PK blood samples will be collected from all subjects on a sparse sampling schedule at Day 1, and Weeks 2, 4, 8 and 12 (or ET visit, if applicable).

At selected study centers, in a subset of approximately 68 subjects who consent, PD blood samples will be collected pre-dose on Day 1 and Week 12 (or ET visit, if applicable). PD samples will be obtained from the same subjects who consent to biopsy collection. An additional PD blood sample will be collected at Week 4 in subjects who also consent to four skin biopsies.

At selected study centers, in a subset of approximately 68 subjects who consent, three or four skin biopsies will be collected during this study. Two 4.5-mm punch biopsies (one from lesional skin and one from adjacent nonlesional skin) will be collected at Day 1, and one 4.5-mm punch biopsy will be collected from the same lesional skin (outside the scar of the previous biopsy, at least 1 cm away from the previous scar) at Week 12 (or ET visit, if applicable). In addition, one 4.5-mm punch biopsy will be collected from the same lesional skin (outside the scar of the previous biopsy, at least 1 cm away from the previous scar) at Week 4 in subjects who consent to four skin biopsies.

At selected study centers, in a subset of approximately 68 subjects who consent, medical photographs of the area of worst AD involvement will be taken to illustrate any visible clinical change.

No formal interim analyses are planned for this study. However, unblinded safety data will be generated and reviewed by a Data and Safety Monitoring Board (DSMB) during the study.

4.2 Scientific Rationale for Study Design

The proposed design is considered appropriate for assessing the efficacy of ASN002 study products compared to a placebo in subjects with AD, and to evaluate the safety and tolerability of ASN002 study product in subjects with atopic dermatitis.

The study will be randomized to ensure random allocation of subjects to treatment arms to reduce bias. Because efficacy assessments of AD have a high degree of subjectivity, the study will be double-blinded. The highest degree of subjects and assessor blinding should be sought to achieve credible inference. It is also important to have a placebo control in a Phase 2 study to control for confounding factors, such as potential investigator bias, and to ensure that the statistical procedures can be appropriately applied.

4.3 End of Study Definition

A subject is considered to have completed the study if he or she has completed all phases of the study, including the last visit or the last scheduled procedure shown in the schedule of events, Table 1.

4.4 Safety Monitoring Criteria for Individual Subject Treatment Interruption/Discontinuation

In the event of an adverse event or laboratory abnormality, individual subject study treatment may be temporary or permanently discontinued based on the Investigator's judgement in accordance with the guidelines described in this section.

Treatment may be resumed upon recovery to baseline or mild levels after the condition leading to suspension of dosing resolves, at the discretion of the principal investigator in consultation with the medical monitor. A decision to temporarily discontinue study drug and/or to reinstitute study treatment should be discussed with the medical monitor. The investigator may suspend study treatment at any time, even without consultation with the medical monitor if the urgency of the situation requires immediate action and if this is determined to be in the subject's best interest. However, the medical monitor should be contacted as soon as possible in any case of study drug discontinuation/interruption. Resumption of study treatment after temporary discontinuation should always be discussed with the medical monitor.

Any retreatment should only be considered upon written agreement between the investigator and the sponsor. This information pertaining to discontinuation or interruption of study medication and the reasons for it must be recorded in the case report form.

No dose reductions or modifications are permitted.

4.4.1 Interruption criteria

A subject who meets either of the below criteria will have the study drug interrupted until laboratory retesting is performed and/or event resolution.

- neutrophils > 0.5 x 10^3 /μL but < 1 x 10^3 /μL;
- platelet count > 50 x 10^3 /μL but < 100 x 10^3 /μL;
- lymphocytes < 0.5 x 10^3 /μL but > 0.2 x 10^3 /μL;
- CPK >10 x ULN;
- an infection requiring IV treatment with antiviral, antibiotic, antiprotozoal, antiparasite or requiring oral medications of those longer than 2 weeks;
- AST/ALT > 5 x ULN*.

*Decision to restart the medication following any laboratory abnormality described above will be made in consultation with the study sponsor and medical monitor.

4.4.2 Permanent study discontinuation

Adverse events or laboratory abnormalities who meet either of the below criteria will result in permanent study discontinuation of the subject. Treatment with the study product will be immediately stopped and the subject withdrawn from this study.

- serious opportunistic infection such as tuberculosis;
- hypertension that cannot be controlled with additional antihypertensive medication(s);
- neutrophils ≤ 0.5 x 10^3 /μL;
- lymphocytes ≤ 0.2 x 10^3 /μL;
- platelets ≤ 50 x 10^3 /μL;
- diagnosis of malignancy;
- venous thrombo-embolic event or major cardiovascular event.

4.5 Data and Safety Monitoring Board

Safety oversight will be under the direction of an independent DSMB composed of individuals with the appropriate expertise. Members of the DSMB should be independent from the study conduct and free of conflict of interest, or measures should be in place to minimize perceived conflict of interest. The DSMB will meet at least three times during the study to assess unblinded safety data on each arm of the study and will provide their recommendations concerning the continuation, modification, or termination of the trial.

5 STUDY POPULATION

5.1 Inclusion Criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria at the screening and Day 1 visits, unless specified otherwise:

1. Male or female subject, aged 18 to 75 years, inclusive, at the time of consent.
2. Subject has clinically confirmed diagnosis of active atopic dermatitis, according to Hanifin and Rajka criteria (Appendix A).
3. Subject has at least a 6-month history of atopic dermatitis and had no significant flares in atopic dermatitis for at least 4 weeks before screening (information obtained from medical chart or subject's physician, or directly from the subject).
4. Subject has an EASI score ≥ 16 at Day 1.
5. Subject has moderate to severe atopic dermatitis at Day 1, as defined by an IGA ≥ 3.
6. Subject has atopic dermatitis covering ≥ 10% of the BSA on Day 1.
7. Subject has a body mass index (BMI) ≤ 38 kg/m^2.
8. Subject has a history of inadequate response to topical corticosteroids or calcineurin inhibitors as treatment for AD within 1 year before the screening visit (information obtained from medical chart or subject history).
9. Subject has been using an emollient (except those containing urea) either once daily or twice daily for at least 1 week prior to Day 1 and agrees to continue using that same emollient, daily and at the same frequency, throughout the study. Note: On the day of scheduled visits, subjects cannot apply emollient before their scheduled visit time.
10. For women of childbearing potential involved in any sexual intercourse that could lead to pregnancy: the subject must agree to use a highly effective contraceptive method from at least 4 weeks before Day 1 until at least 4 weeks after the last study product administration. Highly effective contraceptive methods include hormonal contraceptives (combined oral contraceptive, patch, vaginal ring, injectable, or implant), intrauterine devices or intrauterine systems, vasectomized partner(s), tubal ligation, or double barrier methods of contraception (barrier methods include male condom, female condom, cervical cap, diaphragm, and contraceptive sponge) in conjunction with spermicide.
    Note: Subjects must have been on a stable dose of hormonal contraceptives for at least 4 weeks before Day 1.

    Note: The above list of contraceptive methods does not apply to subjects who are abstinent for at least 4 weeks before Day 1 and will continue to be abstinent from penile-vaginal intercourse throughout the study. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the participant.
    Note: For countries where double barrier methods are not accepted as highly effective contraception, then this option must not be considered.
    Note: A woman of nonchildbearing potential is as follows:

a. Woman who has had surgical sterilization (hysterectomy, bilateral oophorectomy, or bilateral salpingectomy);
b. Woman who has had a cessation of menses for at least 12 months without an alternative medical cause, and a follicle-stimulating hormone (FSH) test confirming nonchildbearing potential (refer to laboratory reference ranges for confirmatory levels).

11. For men involved in any sexual intercourse that could lead to pregnancy, subject must agree to use one of the highly effective contraceptive methods listed in Inclusion Criterion #10, from Day 1 until at least 4 weeks after the last study product administration. If the female partner of a male subject use any of the hormonal contraceptives methods listed above, this contraceptive method must be used by the female partner from at least 4 weeks before Day 1 until at least 4 weeks after the last study product administration.
12. Female of childbearing potential has had a negative serum pregnancy test at screening and negative urine pregnancy test on Day 1.
13. Subject is willing to participate and is capable of giving informed consent. Note: Consent must be obtained prior to any study-related procedures.
14. Subjects must be willing to comply with all study procedures and must be available for the duration of the study.

5.2 Exclusion Criteria

A subject who meets any of the following criteria at the screening and Day 1 visits, unless specified otherwise, will be excluded from participation in this study:

1. Subject is a female who is breastfeeding, pregnant, or who is planning to become pregnant during the study.
2. Subject has clinically infected atopic dermatitis.
3. Subject has a history of skin disease or presence of skin condition that, in the opinion of the investigator, would interfere with the study assessments.
4. Active infection, including skin infection, requiring treatment.
5. Subject has a history of cancer or lymphoproliferative disease within 5 years prior to Day 1. Subjects with successfully treated nonmetastatic cutaneous squamous cell or basal cell carcinoma and/or localized carcinoma in situ of the cervix are not to be excluded.
6. Subject has any clinically significant medical condition or physical/laboratory/ECG/vital signs abnormality that would, in the opinion of the investigator, put the subject at undue risk or interfere with interpretation of study results.
7. Subject has 12-lead ECG abnormalities considered by the investigator to be clinically significant or QTc F $\geq$ 450 milliseconds, regardless of clinical significance, at screening. Abnormal ECG may be confirmed with one repeat assessment. For subjects with QTcF$\geq$450 msec on initial ECG, the mean of the two QTc F assessments will determine eligibility.
8. Subject has a history of congestive heart failure New York Heart Association (NYHA) class III or IV.

9. Subject has a history of erythrodermic, refractory or unstable skin disease, including AD, that requires frequent hospitalizations and/or intravenous treatment for skin infections over the last year
10. Subject has a history of eczema herpeticum within 12 months, and/or a history of 2 or more episodes of eczema herpeticum in the past.
11. Subject has a history of recurrent venous thromboembolic event (VTE) (>=2)
12. Subject has experienced any of the following within the last 6 months prior to Day 1: VTE myocardial infarction, angioplasty, or cardiac stent placement, unstable ischemic heart disease, or stroke.
13. Subject had other major surgery within 8 weeks prior to Day 1 or has a major surgery planned during the study.
14. Subject is known to have immune deficiency or is immunocompromised.
15. Subject has positive results for hepatitis B surface antigens (HBsAg), antibodies to hepatitis B core antigens (anti-HBc), hepatitis C virus (HCV), or human immunodeficiency virus (HIV) at the screening visit.
16. Presence of any of the following laboratory abnormalities at the screening visit:
    a. Hemoglobin < 11 g/dL;
    b. White blood cell (WBC) < 3.0 x 10^3 /μL;
    c. Platelet count < 125 x 10^3 /μL;
    d. Neutrophils < 1.8 x 10^3 /μL;
    e. Lymphocytes < 1.0 x 10^3 /μL;
    f. Aspartate aminotransferase (AST)/alanine aminotransferase (ALT) > 2 x the upper limit of normal (ULN).
    g. Total bilirubin > 1.2 x ULN (except for elevated indirect bilirubin secondary to Gilbert's syndrome);
    h. Creatinine > ULN.
17. Subjects has uncontrolled hypertension within the last 1 month prior to screening or blood pressure at screening of systolic blood pressure >160 mm Hg or diastolic BP >95 mm Hg, confirmed by one repeat assessment.
18. Subject has a known active tuberculosis or a positive tuberculosis (TB) infection test. Subject will be evaluated for latent TB infection with a purified protein derivative (PPD) test or a QuantiFERON-TB Gold test. Subjects who demonstrate evidence of latent TB infection (either PPD ≥5 mm of induration or positive QuantiFERON-TB Gold test, irrespective of bacille Calmette-Guérin vaccination status) will only be allowed to participate in the study if there is documented evidence of a completed adequate treatment course for latent TB (with negative chest x-ray findings for active TB).
19. Subject has difficulty swallowing medications, or known history of malabsorption syndrome.
20. Subject has a history of recurrent gastroesophageal reflux disease (GERD) requiring the use of proton pump inhibitors within the last month.

21. Subject has a known history of diverticulitis.
22. Subject has uncontrolled diabetes.
23. Any medical or psychiatric condition which, in the opinion of the investigator or the sponsor's medical monitor, would place the subject at risk, interfere with participation in the study, or interfere with the interpretation of study results.
24. Subject has used dupilumab within 12 weeks prior to Day 1.
25. Subject has received any UV-B phototherapy (including tanning beds) or excimer laser within 4 weeks prior to Day 1.
26. Subject has had psoralen-UV-A (PUVA) treatment within 4 weeks prior to Day 1.
27. Subject has used doxepin within 1 week prior to Day 1.
28. Subject has used hydroxyzine or diphenhydramine within 1 week prior to Day 1.
29. Subject has used topical products containing urea within 1 week prior to Day 1.
30. Subject has used systemic antibiotics within 2 weeks or topical antibiotics within 1 week prior to Day 1.
31. Subject has used any topical medicated treatment for atopic dermatitis within 2 weeks prior to Day 1, including, but not limited to, topical corticosteroids, crisaborole and any other topical phosphodiesterase-4 inhibitor, calcineurin inhibitors, tars, bleach, antimicrobials, medical devices, and bleach baths.
32. Subject has used systemic treatments (other than biologics) that could affect atopic dermatitis less than 4 weeks prior to Day 1 (e.g., retinoids, calcineurin inhibitors, methotrexate, cyclosporine, hydroxycarbamide [hydroxyurea], azathioprine, oral/injectable corticosteroids). Note: Intranasal corticosteroids, eye drops containing corticosteroids, and inhaled corticosteroids for stable medical conditions are allowed.
33. Subject has received any marketed or investigational biological agent within 12 weeks or 5 half-lives (whichever is longer) prior to Day 1.
34. Subject is currently receiving any other medication for AD.
35. Subject is currently receiving a nonbiological investigational product or device or has received one within 4 weeks prior to Day 1.
36. Subject has excessive sun exposure, is planning a trip to a sunny climate, or has used tanning booths within 4 weeks prior to Day 1, or is not willing to minimize natural and artificial sunlight exposure during the study. Use of sunscreen products and protective apparel are recommended when exposure cannot be avoided.
37. Subject has received a live attenuated vaccine within 4 weeks prior to Day 1 or plans to receive a live attenuated vaccine during the study and up to 4 weeks or 5 half-lives (of the study product), whichever is longer, after the last study product administration.
38. Subject has used ASN002.

39. Subject had prior treatment with a systemic SYK or JAK inhibitor for which the subject received no clinical benefit in the opinion of the investigator, or the subject relapsed whilst on therapy, or was withdrawn for safety reasons.
40. Subject has a known hypersensitivity to ASN002 or its excipients.
41. Subject has a known history of clinically significant drug or alcohol abuse in the last year prior to Day 1.
42. Subject has a close affiliation with the investigator (e.g., a close relative) including any study staff of the sites or persons working at the CRO or subject is an employee of the sponsor.
43. Subject is institutionalized because of legal or regulatory order.
44. Only for subjects consenting to biopsies:
    a. Subject has a history of an allergic reaction or significant sensitivity to lidocaine or other local anesthetics;
    b. Subject has a history of hypertrophic scarring or keloid formation in scars or suture sites;
    c. Subject is taking anticoagulant medication, such as heparin, low molecular weight (LMW)-heparin, warfarin, antiplatelets (except low-dose aspirin which will be allowed), within 2 weeks prior to Day 1, or has a contraindication to skin biopsies. Nonsteroidal anti-inflammatory drugs [NSAIDs] will not be considered antiplatelets and will be allowed.

5.3 Discontinuation and Lost to Follow-Up

Subjects have the right to withdraw from the study at any time for any reason without penalty. The investigator also has the right to withdraw subjects from the study if he or she feels it is in the best interest of the subject or if the subject is uncooperative or noncompliant.

Should a subject decide to withdraw, all efforts will be made to complete and report the observations as thoroughly as possible, particularly the examinations outlined in the ET visit. The investigator or one of his or her staff members should contact the subject to determine as accurately as possible the primary reason for the withdrawal.

A complete final evaluation at the time of the subject's withdrawal should be made with an explanation of why the subject is withdrawing from the study. If the reason for removal of a subject is an AE or an abnormal laboratory test result, the principal specific event or test will be recorded.

If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this written request in the site study records.

5.3.1 Discontinuation

Subjects who discontinue the study after the first dose will be asked, if they agree, to come for a last assessment (ET visit). Subjects who receive an active treatment for AD after Week 4 visit are not necessarily discontinued from the study (refer to section 6.4.2 for more information on how to proceed with these subjects). Subjects who have their study product discontinued due to the start

of a prohibited medication for the treatment of AD or for any other safety reasons will be asked to come back for an additional follow-up visit about 4 weeks after the study product discontinuation (in addition to the ET visit).

Subjects who did not complete the study for reasons other than safety, or have demonstrated significant noncompliance to study treatments based on IP accountability (define as subject who received <80% or >120% of the scheduled doses during the study treatment period) will be evaluated by the principal investigator or designee at each visit and may potentially be replaced. If a subject drops out during the first 4-week period, the subject may be replaced at sponsor's discretion.

Reasons for discontinuation include the following:

- The investigator decides that the subject should be withdrawn. If this decision is made because of a serious adverse event (SAE), the study product is to be discontinued in that subject immediately and appropriate measures are to be taken. The investigator will notify the sponsor immediately.
- The attending physician requests that the subject be withdrawn from the study.
- The subject, for any reason, requires treatment with another therapeutic agent may be discontinued as detailed in section 6.4.2.
- The subject is lost to follow-up. In this case, a reasonable attempt to contact the subject and ascertain his or her status must be made, and these attempts must be documented.
- The subject becomes pregnant at any time during the study.
- The subject may withdraw from the study for any other reason, including withdrawal of consent.
- The sponsor or regulatory authorities, for any reason, stop the study. In this case, all subjects will be discontinued from the study. The investigator will immediately, on discontinuance of the study by the sponsor, in its entirety or at a clinical trial site, inform both the subjects and the research ethics board of the discontinuance, provide them with the reasons for the discontinuance and advise them in writing of any potential risks to the health of subjects or other persons.

5.3.2 Lost to Follow-Up

A subject will be considered lost to follow-up if he or she fails to return for scheduled visits and is unable to be contacted by the study site staff.

The following actions must be taken if a subject fails to return to the clinic for a required study visit:

- The site will attempt to contact the subject and reschedule the missed visit. The site will then counsel the subject on the importance of maintaining the assigned visit schedule and ascertain if the subject wishes to or should continue in the study.
- Before a subject is deemed lost to follow-up, the investigator or designee will make every

effort to regain contact with the subject (where possible, three telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record or study file.

- If all attempts to contact the subject fail, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

5.4 Screen Failures

Screen failures are defined as individuals who consent to participate in the clinical trial, but are not subsequently randomly assigned to the study products. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAEs.

Individuals who do not meet the criteria for participation in this trial (screen failure) may be rescreened once, if deemed acceptable by the investigator. Rescreened subjects should be assigned a different subject number than the initial screening. All procedures planned at the screening visit, including signature of a new consent form, will be performed.

Subjects who do not qualify to participate in the study due to a screening laboratory value abnormality can repeat the test once within the original screening time window without resulting in screen failure, if the investigator believes there is a reasonable possibility that the subject would be eligible if re-tested.

6 TREATMENT

6.1 Study Products Administered

This study involves 3 different doses of ASN002 (40 mg, 60 mg, and 80 mg) orally administered once daily compared to a placebo. ASN002 will be available in 20-mg strength tablets. All study products will be provided by the sponsor.

All study products will be administered orally daily at approximately every 24 hours, as assigned, for 12 weeks on an empty stomach (2 hours before and 2 hours after a meal) with approximately 240 mL of water. On visit days, the study products will be administered at the study site. The date and time of the drug administration and fasting conditions will be collected daily by the study site or via a diary provided to the subject. The subject should be instructed to take the study product at approximately the same time of the day.

Further details regarding the study products can be found in Table 2.

Table 2. Study Products

	Study Products			
Product name	**ASN002**	**ASN002**	**ASN002**	**Placebo**
Dosage form	Tablet	Tablet	Tablet	Tablet
Unit dose strength(s)	20 mg	20 mg	20 mg	N/A
Dosage level(s)	40 mg	60 mg	80 mg	N/A
Number of tablets per dose level	2 active 2 placebo	3 active 1 placebo	4 active	4 placebo
Route of Administration	Oral	Oral	Oral	Oral
Dosing instructions	Once a day with approximately 240 mL of water	Once a day with approximately 240 mL of water	Once a day with approximately 240 mL of water	Once a day with approximately 240 mL of water
Source of procurement	Asana BioSciences, LLC	Asana BioSciences, LLC	Asana BioSciences, LLC	Asana BioSciences, LLC

The contents of the label will be in accordance with all applicable regulatory requirements.

6.1.1 Missed or Vomited Doses

Should the subject forget to take the study product, she/he should take the study product as soon as she/he remembers up to 6 hours after the planned dosing time. Thereafter, the forgotten dose should not be taken and the next dose should be taken as per the originally planned schedule. Vomited doses should not be retaken.

6.1.2 Duration of Treatment

The maximum treatment duration per subject is 12 weeks.

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Preparation/Storage/Handling

All study products must be stored in a secure environmentally controlled and monitored area in accordance with the labelled storage conditions with access limited to the investigator and authorized site staff. The study product(s) may only be supplied by authorized site staff and may only be given to subjects enrolled into the study.

Study product(s) will be dispensed by the study site to the subject at the visits specified in Table 1. Subjects are to return all study product (used and unused) to the study site. The tablets will be counted prior to dispensing and upon return, and the counts will be recorded in the source documents. Each subject will be instructed on the importance of returning study product at the next study visit and on taking the product as prescribed. If a subject does not return study product, he or she will be instructed to return it as soon as possible.

6.2.2 Accountability

The investigator is responsible for maintaining accurate records of the study product received initially and of the study product dispensed/used. After verification of the study product accountability by the sponsor or designee, used product will be stored safely until destruction/return. Any study product accidentally or deliberately destroyed, or returned to the sponsor or designee will be accounted for. Any discrepancies between amounts dispensed and returned will be explained.

All study product accountability forms and treatment logs must be retained in the investigator's study files. Product inventory and accountability records will be maintained as per ICH GCP. These records must be available for inspection at any time by the sponsor, its designees, or by regulatory agencies.

Further guidance and information for final disposition of study products are provided in the study manual.

6.3 Randomization

At the investigational site, each screened subject will be assigned a subject identifier number during screening that will be used on all subject documentation. The subject identifier number will contain the site number and the subject number and will be assigned in numerical order at the screening visit based on chronological order of screening dates (e.g., 002-010 for the 10th subject screened at the Site #002).

Approximately 220 subjects will be randomized in a 1:1:1:1 ratio to receive either ASN002 40 mg, 60 mg, or 80 mg, or placebo, in order to complete the study with 160 evaluable subjects.

Randomization will occur prior to first dosing, at Day 1 visit. The randomization list will be generated using a validated software. Randomization will be stratified by baseline disease severity at Day 1 ([EASI = 16.0-21.2] vs. [EASI = 21.3-29.9] vs. [EASI = ≥ 30.0]) and biopsy collection. The master randomization list will be kept secured until the study blind is broken at the end of study. This list will be uploaded into an Interactive Web Response System (IWRS). The investigator or designee will be able to acquire a randomization number for eligible subjects by connecting to the IWRS.

Further guidance and information can be obtained in the study manual.

6.3.1 Blinding

This study will be double-blinded. At all times, treatment and randomization information will be kept confidential and will not be released to the investigator, the study staff, the contract research organization (CRO), or the sponsor's study team until after the conclusion of the study.

Safety oversight will be under the direction of an independent DSMB, who will remain unblinded during the study.

Blinding codes should only be broken in emergency situations for reasons of subject safety. If unblinding the treatment assignment for a subject is necessary due to a medical emergency (an unexpected SAE per product's safety profile) and other significant medical situations such as pregnancy, the investigator can make the decision to unblind the treatment assignment if knowing the treatment assignment will help treatment decision of the particular AE. When the blind for a subject has been broken, the reason must be fully documented in the source document and eCRF. Whenever possible, the investigator should contact the sponsor or its designee before breaking the blind. If the blind is broken, the investigator should promptly inform the medical monitor. Documentation of breaking the blind should be recorded with the date/time and reason why the blind was broken, and the names of the personnel involved.

Emergency unblinding details are provided in the study manual.

The subject for whom the blind has been broken will be discontinued from the study and undergo the ET procedures. In cases where there are ethical reasons to have the subject remain in the study, the investigator must obtain specific approval from the sponsor or its designee for the subject to continue in the study. The primary reason for discontinuation (the event or condition which led to the unblinding) will be recorded.

6.3.2 Study Product Compliance

Study product compliance will be monitored at each visit. Adherence to treatment will be assessed by direct questioning, review of the subject's dosing diary, and by maintaining adequate study

product dispensing and return records. Any deviation from the prescribed dosage regimen will be recorded in the source document and eCRF.

Subjects who are significantly noncompliant with treatment based on IP accountability will be counseled and could be discontinued from the study, at the discretion of the investigator, following consultation with the sponsor. A subject will also be considered significantly noncompliant if he or she intentionally or repeatedly takes more than the prescribed amount of study product in the same time frame, as judged by the investigator.

6.4 Concomitant Therapy

All medications (including over-the-counter drugs, vitamins, herbal/natural products and antacids) taken within 4 weeks prior to screening and throughout the study must be recorded.

Medication entries may be captured as generic or trade names. Trade names should be used for combination drugs. Entries should include as much as possible of the following information: the dose, unit, frequency of administration, route of administration, start date, discontinuation date, and indication. If the medication is discontinued or the dosage is changed, these details must be recorded.

6.4.1 Permitted Therapies

Subjects must apply an emollient of their choice (except those containing urea) on their skin. The emollient use must be initiated at least 1 week prior to study Day 1 and must be kept at the same frequency (once or twice daily) throughout the study until the follow-up visit at Week 16. However, on the day of scheduled visits, subjects cannot apply emollient before their scheduled visit time.

Every effort should be made to keep the same emollient throughout the study. The commercial name of the selected emollient(s) will be recorded in the source document and the eCRF. No other products may be applied to the lesions during the study. Emollient use will be followed daily in the subject diary.

Use of sunscreen products and protective apparel are permitted when exposure cannot be avoided.

6.4.2 Prohibited Therapies or Procedures

Table 3 lists prohibited medications that are not to be used from the defined washout periods before the first administration of study products at the Day 1 visit through the last study visit.

The discretionary use of concomitant treatments or therapies for atopic dermatitis is prohibited between Day 1 and Week 16 visit. However, should subjects experience an exacerbation of atopic dermatitis that requires, in the opinion of the investigator, the use of a prohibited therapy, the following approach should be followed:

1. The investigator needs to discuss the case with the medical monitor in order to obtain permission to use a prohibited medication.
2. Subjects who start prohibited medications as a treatment for AD within the first 4 weeks of the study will be discontinued from the study product (ASN002 or placebo) and will perform the ET visit at the time of discontinuation. In addition, the subject will be asked to come back for a follow-up visit 4 weeks after the study product is stopped. Collection of PD samples, PK samples, and skin biopsies will not be performed after the ET visit. These subjects will not be eligible to participate in the OLE study.
3. Subjects who start prohibited topical medications as a treatment for AD after the first 4 weeks of the study may continue all the study assessments up to the last study visit. Treatment with the study product may continue concurrently until the end of the treatment period, and these subjects will be eligible to participate in the OLE study afterwards. Collection of PD samples and skin biopsies will not be performed after the start of a topical medication.
4. Subjects who start prohibited oral corticosteroids as a treatment for AD after the first 4 weeks of the study will be discontinued from the study product (ASN002 or placebo). Use of oral corticosteroids after permanent cessation of ASN002 is permitted only for a short period of time (maximum 3 weeks). Subjects should come to all planned study visits for safety assessments up to the Week 12 visit. Collection of PD samples, PK samples, and skin biopsies will not be performed after study product discontinuation. These subjects will be eligible to participate in the OLE study if they meet the required washout period for prohibited medications as defined in the OLE study.
5. Subjects who start any other prohibited systemic medications as a treatment for AD after the first 4 weeks of the study will be discontinued from the study product (ASN002 or placebo) and will perform the ET visit at the time of discontinuation. In addition, the subject will be asked to come back for a follow-up visit 4 weeks after the study product is stopped. Collection of PD samples, PK samples, and skin biopsies will not be performed after the ET visit. These subjects may be eligible to participate in the OLE study not earlier than 12 weeks after Day 1 of the present study and only if they meet the required washout period for prohibited systemic medications as defined in the OLE study.
6. Subjects who start any other prohibited medications or therapies for other reasons may be withdrawn from the study, at the investigator's discretion in agreement with the medical monitor and the sponsor.

If in any doubt, investigators are advised to discuss medications with the medical monitor.

Table 3. Prohibited Therapies or Procedures

Prohibited medications, products, and procedures	Washout period prior to first dose (Day 1)
Any marketed or investigational biological agent	12 weeks or 5 half-lives (whichever is longer)
Dupilumab	12 weeks
Nonbiological investigational product or device	4 weeks
Live attenuated vaccine	4 weeks
Systemic treatments (other than biologics) that could affect atopic dermatitis (e.g., retinoids, calcineurin inhibitors, methotrexate, cyclosporine, hydroxycarbamide [hydroxyurea], azathioprine, oral/injectable corticosteroids) Note: Intranasal corticosteroids, eye drops containing corticosteroids, and inhaled corticosteroids for stable medical conditions are allowed	4 weeks
PUVA treatment, UV-B phototherapy (including tanning beds) or excimer laser, excessive sun exposure or has used tanning booths	4 weeks
Topical medicated treatment for atopic dermatitis including, but not limited to, topical corticosteroids, crisaborole and any other topical phosphodiesterase-4 inhibitor, calcineurin inhibitors, tars, bleach, antimicrobials, medical devices, and bleach baths	2 weeks
Systemic antibiotics	2 weeks
Topical antibiotics*	1 week
Topical products containing urea	1 week
Hydroxyzine and diphenhydramine	1 week
Doxepine	1 week

*Use of topical antibiotics on biopsy site only is allowed.

6.4.3 Concomitant Use of Drugs that may affect Gastric pH

The use of antacids and H2 antagonists should be considered in place of proton pump inhibitors in subjects receiving ASN002. However, H2 antagonists and aluminum or magnesium containing antacids may only be taken within a 3-10-hour window following dosing with ASN002. Refer to Table 4 for a sample list of concomitant medications that may affect gastric pH.

Table 4. Examples of H2 antagonists and Proton Pump Inhibitors

Prohibited	Permitted	
Proton Pump Inhibitors	**H2 antagonists**	**Antacids**
Esomeprazole/ omeprazole	cimetidine	Aluminum-based antacids
lansoprazole	nizatidine	Magnesium-based antacids
pantoprazole	ranitidine	Calcium-based antacids
rabeprazole		
The examples provided are not an exhaustive list of possible drugs that may affect gastric pH. The investigator is responsible for assessing all concomitant medications that may have effects on gastric pH.		

6.4.4 Study Restrictions

Subject should be willing to minimize natural and artificial sunlight exposure during the study. Use of sunscreen products and protective apparel are recommended when exposure cannot be avoided.

7 STUDY ASSESSMENTS AND PROCEDURES

7.1 Efficacy Assessments

Clinical evaluations of atopic dermatitis will be performed by an experienced and qualified dermatologist (board certified or equivalent) or other suitably qualified and experienced designee. To assure consistency and reduce variability, the same assessor should perform all assessments on a given subject whenever possible.

7.1.1 Eczema Area and Severity Index

The Eczema Area and Severity Index (EASI) will be assessed at the visits specified in Table 1 before the study product administration. It quantifies the severity of a subject's atopic dermatitis based on both lesion severity and the percentage of BSA affected (18). The EASI is a composite score ranging from 0 to 72 that takes into account the degree of erythema, induration/infiltration (papules), excoriation, and lichenification (each scored from 0 to 3 separately) for each of four body regions, with adjustment for the percentage of BSA involved for each body region and for the proportion of the body region to the whole body. A detailed procedure of EASI score calculation is provided in Appendix B. To be eligible for this study, subjects must have an EASI score of ≥16 at Day 1.

7.1.2 Investigator Global Assessment

The Investigator Global Assessment (IGA) of disease severity will be assessed at the visits specified in Table 1 before the study product administration. The IGA is a global assessment of the current state of the disease. It is a 5-point morphological assessment of overall disease severity. A detailed description of the IGA scale is provided in Appendix C. To be eligible for this study, subjects must have an IGA score of ≥3 at Day 1.

7.1.3 SCORing Atopic Dermatitis

The SCORing Atopic Dermatitis (SCORAD) will be measured at the visits specified in Table 1 before the study product administration. The SCORAD grading system was developed by the European Task Force on Atopic Dermatitis (1993) and has been a standard tool to assess AD severity in clinical studies in Europe (19, 20). Six items (erythema, edema/papulation, oozing/crusts, excoriation, lichenification, and dryness) will be evaluated the AD severity. The overall BSA affected by AD will be evaluated (from 0% to 100%) and included in the SCORAD scores. Loss of sleep and pruritus will be evaluated by subjects on a visual analog scale (0-10) and should be based on the average of the last three days/nights. The sum of these measures represents the SCORAD, which can range from 0 to 103. The detailed procedure of SCORAD score calculation is provided in Appendix D.

7.1.4 Body Surface Area

The overall Body Surface Area (BSA) affected by AD will be evaluated (from 0% to 100%) at the visits specified in Table 1 before the study product administration. One subject's palm represents

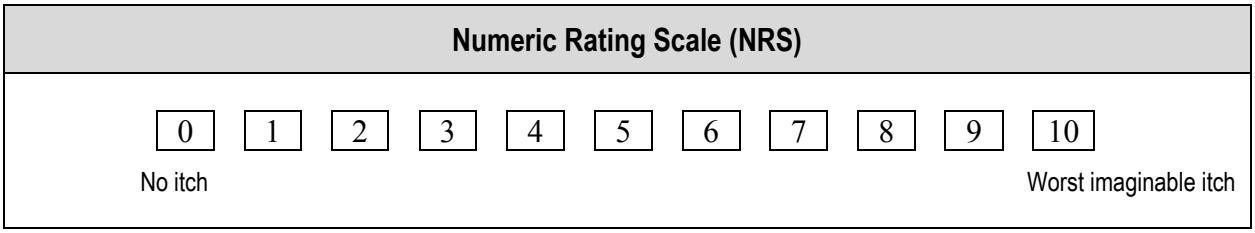
1% of his or her total BSA. For all study visits except at screening, the BSA of involved skin will be measured with the SCORAD measurement (Section 7.1.3) and evaluated as a separate endpoint. To be eligible, subjects must have a BSA of ≥10% at Day 1.

7.1.5 Pruritus Numeric Rating Scale

The intensity of pruritus will be recorded for the entire duration of the treatment (daily) as specified in Table 1 using a numeric rating scale (NRS) (21). This will be evaluated by asking subjects to assign a numerical score representing the worst intensity over the last 24 hours of their symptoms on a scale from 0 to 10, with 0 indicating no symptoms and 10 indicating the worst imaginable symptoms. The pruritus NRS is presented in Figure 2.

Subjects will record the pruritus NRS in a diary before the study product administration. Subject compliance on the pruritus NRS will be followed at each clinic visit.

Figure 2: Pruritus Numeric Rating Scale



7.1.6 5D-Pruritus Scale

The 5-D Pruritus Scale will be evaluated at the visits specified in Table 1. The 5-D Pruritus Scale is a 1-page, 5-question, validated questionnaire used in clinical trials to assess 5 dimensions of background itch: degree, duration, direction, disability, and distribution (22). Each question corresponds to 1 of the 5 dimensions of itch; subjects will rate their symptoms over the preceding 2-week period as "present" or on a 1 to 5 scale, with 5 being the most affected.

The 5-D Pruritus Scale is provided in Appendix E.

7.2 Quality-of-Life Assessments

7.2.1 Patient-Oriented Eczema Measure

The Patient-Oriented Eczema Measure (POEM) will be assessed at the visits specified in Table 1. The POEM developed by Charman et.al. (23, 24) is a self-assessment of disease severity by the subject. The POEM has a maximum value of 28 based on the subject's response to seven questions scored from 0 to 4. A detailed description of the POEM assessment is provided in Appendix F.

7.2.2 Dermatology Life Quality Index Questionnaire

The Dermatology Life Quality Index (DLQI) will be assessed at the visits specified in Table 1. It is a simple 10-question validated questionnaire that has been used in more than 40 different skin conditions. Its use has been described in more than 1,000 publications, including many multinational studies. The DLQI is the most frequently used instrument in studies of randomized controlled trials in dermatology. The questionnaire is provided in Appendix G.

7.3 Safety Assessments

7.3.1 Vital Signs

The following vital signs will be recorded at the visits specified in Table 1 with the subject in a seated position, after having sat calmly for at least 5 minutes: systolic and diastolic blood pressure (mmHg), pulse (bpm), and body temperature (°C).

Weight (kg) and height (cm) will be collected to calculate the BMI and will be recorded at the visits specified in Table 1. The height will only be recorded at the screening visit and the same value will be used for BMI calculation at other visits.

If deemed appropriate by the investigator, clinically significant findings in the vital signs will exclude a subject from study participation. Any abnormal finding related to vital signs that the investigator considers to be clinically significant must be recorded as an AE.

7.3.2 Physical Examination

The following sites/systems will at least be included in the physical examination, which will be performed at the visits specified in Table 1:

- General appearance
- Dermatological (except atopic dermatitis)
- Head, eyes, ears, nose, throat (HEENT)
- Respiratory
- Cardiovascular
- Abdominal
- Neurological
- Musculoskeletal
- Lymphatic

Information for all physical examinations must be included in the source document. If deemed appropriate by the investigator, clinically significant findings in the physical examination will exclude a subject from study participation. Any significant change will be reported as an AE in the source document and eCRF.

7.3.3 Brief Physical Examination

The following sites/systems will at least be included in the brief physical examination that will be performed at the visits specified in Table 1:

- General appearance
- Dermatological (except atopic dermatitis)
- Respiratory
- Cardiovascular
- Abdominal

Information for all physical examinations must be included in the source document. If deemed appropriate by the investigator, clinically significant findings in the physical examination will exclude a subject from study participation. Any significant change will be reported as an AE in the source document and eCRF.

7.3.4 Clinical Laboratory Tests

Laboratory tests will be performed at the visits specified in Table 1. The tests will include urinalysis, hematology with differential, a standard chemistry panel (chemistry includes liver function tests and cholesterol), and serum pregnancy test (screening) for women of childbearing potential (WOCBP). At the visit specified in Table 1, a urine pregnancy test will be performed for WOCBP (conducted at the investigator site). The specific tests in these panels are listed in Table 5.

Table 5: Clinical Laboratory Testing

Laboratory Testing	Tests Included
Hematology	HCT, Hgb, MCH, MCHC, MCV, MPV, PLT, RBC, reticulocyte count, WBC, and differentials (neutrophils, lymphocytes, monocytes, eosinophils, and basophils relative and absolute)
Biochemistry	Albumin, alkaline phosphatase, ALT, AST, calcium, carbon dioxide, chloride, creatinine (enzymatic), CPK, GGT, glucose random, LDH, lipid panel (HDL, LDL, total cholesterol and triglycerides (non-fasting)), phosphorus, potassium, sodium, total bilirubin, TBIL (direct bilirubin reflex if elevated), urea (BUN), uric acid, CRP, total protein
Urinalysis	Color, clarity, pH, specific gravity, bilirubin, glucose, ketones, leukocytes, nitrite, blood, protein, urobilinogen and microscopic analysis (as required)
Urine pregnancy test	For females of childbearing potential (at each visit, except screening)
Laboratory tests required at screening only	β-hCG for females of childbearing potential FSH levels for women who have had a cessation of menses for at least 12 months without an alternative medical cause Tuberculosis test (PPD or QuantiFERON-TB Gold) Serology (HBV (HBsAg, anti-HBc), HCV, HIV)

ALT = alanine aminotransferase; anti-HBc = antibody to hepatitis B core antigen; AST = aspartate aminotransferase; β-hCG = β-human chorionic gonadotropin; BUN = blood urea nitrogen; CPK = Creatine phosphokinase; CRP = C-reactive protein; FSH = follicle-stimulating hormone; GGT = gamma-glutamyl-transferase; HBsAg = hepatitis B surface antigens; HBV = hepatitis B virus; HCT = hematocrit; HCV = hepatitis C virus; HDL = high-density lipoproteins; Hgb = hemoglobin; HIV = human immunodeficiency virus; LDH = lactate dehydrogenase; LDL = low-density lipoproteins; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; MPV = mean platelet volume; PLT = platelets; PPD = purified protein derivative; RBC = red blood cell (count); WBC = white blood cell (count).

Subjects who do not qualify to participate in the study due to a screening laboratory value abnormality can repeat the test once within the original screening time window, if the investigator believes there is a reasonable possibility that the subject would be eligible if re-tested.

If deemed appropriate by the investigator, clinically significant findings in clinical laboratory testing will exclude a subject from study participation. Any significant change will be reported as an AE.

7.3.5 Electrocardiogram

Twelve-lead ECGs will be performed as a safety assessment at the visits specified in Table 1. Clinically significant findings in the ECG should exclude a subject from study participation (as deemed appropriate by the investigator). Any significant change will be reported as an AE.

7.4 Pharmacokinetic and Pharmacodynamic Assessments

7.4.1 Pharmacokinetics Assessments

Blood samples will be collected for PK assessment on visits and time points indicated in the schedule of events in Table 1. Measurement of plasma concentrations of ASN002 will be performed in all subjects receiving ASN002 treatment. A few samples from each of the placebo subjects (e.g., pre-dose on Day 1 and 2 hours at Week 4) may be analyzed for quality control purposes.

The actual date and time of each blood sample collection will be recorded. Approximately 4 mL of blood will be collected for each time point.

Details about the collection, processing, handling, storage and shipping of blood samples will be provided in the laboratory manual.

Non-compartmental PK analysis will not be performed for this study.

Population PK analysis will be performed using nonlinear mixed-effects modeling approach with first-order conditional methods. This analysis may be combined with PK concentrations from other clinical trials in healthy and AD subjects as appropriate. The results from this analysis may be reported separately.

7.4.2 Pharmacodynamics Assessments

At selected study centers, for a subset of approximately 68 subjects who consent to the procedure, blood samples will be collected for PD analysis on visits indicated in the schedule of events in Table 1. PD samples will be drawn as trough samples prior to the study product administration. PD samples will be obtained from the same subjects who consent to biopsy collection.

The actual date and time of each blood sample collection will be recorded. Approximately 8 mL of blood will be collected for each time point.

Details about the collection, processing, handling, storage and shipping of blood samples will be provided in the laboratory manual.

7.4.3 PK/PD Relationship Assessments

PK-efficacy, PK-safety and PK-biomarkers relationships will be explored using linear regression, loess plots, Hills functions, or logistic regression, as appropriate. The results from these analyses may be reported separately.

7.4.4 Skin Biopsies

At selected study centers, for a subset of approximately 68 subjects who consent to the procedure, three or four optional skin biopsies will be collected at the visits specified in Table 1. Two 4.5-mm punch biopsies (one from lesional skin and one from adjacent nonlesional skin) will be collected at Day 1, and one 4.5-mm punch biopsy will be collected from the same lesional skin (outside the scar of the previous biopsy, at least 1 cm away from the previous scar) at Week 12 or ET visit (if applicable). In addition, one 4.5-mm punch biopsy will be collected from the same lesional skin (outside the scar of the previous biopsy, at least 1 cm away from the previous scar) at Week 4 in subjects who consent to four skin biopsies. Biopsy samples will be obtained from the same subjects who consent to PD samples.

The skin will be cleaned, disinfected, and anesthetized before skin biopsies are performed. Sterile gauze will be used to absorb any bleeding. The biopsy sites will be sutured if necessary.

Each biopsy will be split in half. One part will be used for a limited immunohistochemistry panel and the other part will be used for gene expression analysis.

Details about the collection, processing, handling, storage and shipping of biopsy samples will be provided in the laboratory manual.

7.5 Other Assessments

7.5.1 Medical Photography

At selected study centers, for a subset of approximately 68 subjects who consent to the procedure, medical photographs will be performed at the visits specified in Table 1. Photographs of the area of worst eczema involvement will be taken to illustrate any visible clinical change. A target area for each participant will be identified at Day 1, and the same area will be photographed at the other visits. Care will be taken to use the same camera, the same magnification, and the same settings for each photograph at each visit in order to obtain comparable pictures. Medical photographs will be taken using a blue background.

Photographs will be identified and stored as instructed in the photography manual.

7.6 Adverse Events and Serious Adverse Events

7.6.1 Definition of Adverse Event

An AE is any untoward medical occurrence in a subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a study product, whether or not considered related to the study product. AEs and SAEs will be collected from the time of informed consent signature until the final visit / contact.

7.6.2 Definition of Treatment-Emergent Adverse Event

A TEAE is any condition that was not present prior to treatment with the study product but appeared following treatment, was present at treatment initiation but worsened during treatment, or was present at treatment initiation but resolved and then reappeared while the individual was on treatment (regardless of the intensity of the AE when the treatment was initiated).

7.6.3 Definition of Serious Adverse Event

A serious adverse event or reaction is any untoward medical occurrence that, at any dose has any of the following consequences:

- Results in death
- Is life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect

Note: The term “life-threatening” in the definition of “serious” refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

7.6.4 Classification of an Adverse Event

7.6.4.1 Relationship to Study Product

The investigator will establish causality of the AE to the experimental treatment. The investigator should take into account the subject's history, most recent physical examination findings, and concomitant medications.

The degree of "relatedness" of the AE to the study medication must be described using the following scale:

Not related indicates that there is not a reasonable possibility for relationship of the event to the study medication.

Possibly related indicates that a direct cause and effect relationship between study medication and the AE has not been demonstrated, but there is evidence to suggest there is a reasonable possibility that the event was caused by the study medication.

Probably related indicates that there is evidence suggesting a direct cause and effect relationship between the AE and the study medication.

The statement "**reasonable possibility for relationship**" meaning that there are facts (e.g., evidence such as de-challenge/re-challenge/temporal relationship, exposure, likely cause due to known safety profile etc) to suggest a positive causal relationship. The investigators may also change their opinion for causality after follow-up information and may provide a follow-up SAE report with the revised causality assessment.

7.6.4.2 Adverse Event Severity

The intensity of an AE is an estimate of the relative severity of the event made by the investigator based on his or her clinical experience and familiarity with the literature. The following definitions are to be used to rate the severity of an AE:

- Mild: The symptom is barely noticeable to the subject and does not influence performance of daily activities. Treatment is not ordinarily indicated.

- Moderate: The symptom is sufficiently severe to make the subject uncomfortable, and performance of daily activities is influenced. Treatment may be necessary.

- Severe: The symptom causes severe discomfort, and daily activities are significantly impaired or prevented. Treatment may be necessary.

7.6.4.3 Expectedness

The expectedness of each SAE in relation to the study product will be determined, in consultation with the Sponsor when necessary.

7.6.5 Time Period and Frequency for Event Assessment and Follow-Up

The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews of a study subject presenting for medical care, or upon review by a study monitor.

All AEs, including local and systemic reactions, will be captured on the appropriate eCRF. Information to be collected includes event description, date of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and date of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship.

Before subject enrollment, study site personnel will note the occurrence and nature of each subject's medical condition(s) in the appropriate section of the source document and eCRF. During the study, site personnel will note any change in the condition(s) and the occurrence and nature of any AE.

Any medical condition that is present at the time of consent signature will be considered as part of medical history and not reported as an AE. However, if the study subject's condition deteriorates after the consent signature, it will be recorded as an AE.

If a subject experiences an AE at any time after the informed consent signature until the end of participation in the study, the event will be recorded as an AE in the source document and eCRF. Any SAE related to the study participation (e.g., screening procedure) will be recorded in the source document and eCRF from the time a subject consents to participate in the study until the end of participation in the study.

The investigator is responsible for appropriate medical care of subjects during the study. The investigator also remains responsible for following through with an appropriate health care option for all AEs that are ongoing at the end of the study. The subject should be followed until the event is resolved or stable. If an AE is ongoing at the end of study, the follow-up duration is left to the discretion of the investigator. Follow-up frequency will be performed at the discretion of the investigator.

Whenever possible, clinically significant abnormal laboratory results are to be reported using the diagnostic that resulted in the clinically significant abnormal laboratory results and not the actual abnormal test.

Worsening of atopic dermatitis is captured by efficacy assessments and will not be recorded as an AE.

7.6.6 Adverse Event Reporting

Investigators are responsible for monitoring the safety of subjects who are participating in this study and for alerting the sponsor of any event that seems unusual, even if this event may be considered an unanticipated benefit to the subject.

7.6.7 Serious Adverse Events Reporting

Mapi Life Sciences (Mapi) will be responsible for the overall pharmacovigilance process for this study. All SAEs, related to the experimental treatment or not, occurring during the course of the study must be reported on an SAE form to Mapi (see below) within 24 hours of the knowledge of the occurrence (this refers to any AE that meets one or more of the aforementioned serious criteria). The SAE reporting period ends at the end of the follow-up period or if the subject begins an alternative therapy.

Reporting should be done by sending the completed SAE form to the following e-mail address (faxing can also be done as a second option in case e-mailing is not possible).

Safety Contact Information: Mapi
E-mail: innovaderm@pharmacovigilance.center
Fax: (905) 689-1465

Mapi will inform the sponsor, primary medical monitor, and CRO within 1 business day of awareness of a new SAE. Mapi will process and evaluate all SAEs as soon as the reports are received. For each SAE received, Mapi will make a determination as to whether the criteria for expedited reporting to relevant regulatory authorities have been met. Mapi will manage the AE reporting, including suspected unexpected serious adverse reactions, in accordance with the applicable local regulations. SAEs will be reported to the IRB/EC as per local IRB/EC requirements.

The study sponsor will be responsible for notifying the Food and Drug Administration (FDA) of any unexpected fatal or life-threatening suspected adverse reactions as soon as possible, but in no case later than 7 calendar days after the sponsor's initial receipt of the information. In addition, the sponsor must notify the FDA and all participating investigators in an Investigational New Drug (IND) safety report of potential serious risks, from clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days after the sponsor determines that the information qualifies for reporting.

7.6.8 Pregnancy Reporting

If a female subject or a female partner of a male subject becomes pregnant during the study, the subject should inform the study site as soon as possible. Upon confirmation of the pregnancy, the female subject will be discontinued from the study. The investigator must complete a study-specific pregnancy form upon confirmation of a pregnancy and send it to Mapi within 24 hours of confirmation of the pregnancy (contact information to be used is the same as for SAE reporting). Mapi will report all cases of pregnancy to the sponsor and CRO in a timely manner. Posttreatment follow-up should be done to ensure subject safety. Pregnancy is not itself an AE or SAE; however, maternal/fetal complications or abnormalities will be recorded as AEs or SAEs, as appropriate. The investigator will follow the pregnancy until completion or until pregnancy termination and, in the case of a live-born offspring, to 1 month of age in that infant. The investigator will notify Mapi and CRO of the outcome as a follow-up to the initial pregnancy form. All pregnancies should be reported to the sponsor and, when applicable, to the ethics committee.

In the case of an SAE or pregnancy, the subject treatment assignment may be unblinded if judged necessary by the investigator and/or medical monitor in consultation with the sponsor. Once the subject treatment assignment is unblinded, the subject for whom the blind has been broken will be discontinued from the study and undergo the ET procedures.

7.6.9 Overdose

Study drug overdose is any accidental or intentional use of study drug in an amount higher than the dose indicated per protocol for a given subject. Study drug compliance (see section 6.3.2) should be reviewed to detect potential instances of overdose (intentional or accidental).

Any study drug overdose during the study should be recorded on the source document and eCRF. In the event of overdose, the subject should be closely monitored for any potential AEs. All AEs associated with an overdose should be entered on the Adverse Event eCRF and reported using the procedures detailed in section 7.6.7, Serious Adverse Events Reporting, even if the events do not meet seriousness criteria. If the AE associated with an overdose does not meet seriousness criteria, it must still be reported using the SAEs reporting procedures and in an expedited manner, but should be noted as non-serious on the form and the Adverse Event eCRF. The excess quantity and duration of the overdose should be recorded.

8 STATISTICAL CONSIDERATIONS

8.1 Sample Size Determination

Using the following assumptions for the primary efficacy endpoint: a change-from-baseline in EASI at week 12 of at least -15 in the ASN002 dosing groups, a change-from-baseline of -8 in the placebo group, a common standard-deviation of 8, nominal alpha of 0.0167 for each comparison of interest, we would need 40 evaluable subjects per group in order to achieve a power of 92% on the primary efficacy endpoint.

Moreover, with 46 subjects per group, we would have 80% power to show a statistically significant difference between the higher dosing group and placebo in IGA responses (one of the key secondary efficacy endpoint), assuming a response of 37.5% vs. 11.1% in the higher dosing and placebo groups, respectively, using an alpha of 5%.

Thus, assuming about 15% dropout rate, 55 subjects per group will need to be enrolled in this trial for a total of 220 subjects in order to have a minimum of 46 subjects per group to evaluate efficacy with adequate power.

8.2 Populations for Analyses

Modified Intent-to-Treat Population (mITT): This population will include all subjects who received at least one dose of the study product. All subjects will be analyzed according to the treatment group to which they were randomized. The mITT population will be used as the primary analysis population for efficacy.

The Per Protocol Population (PP): This population will include all subjects who were randomized, who received at least one dose of study product, with no significant protocol deviations, and who provided evaluable data for the primary endpoint. All subjects will be analyzed according to the treatment group that they actually received.

The Safety Population (SAF): This population will include all subjects who received at least one dose of the study product. All subjects will be analyzed according to the treatment group that they actually received.

The PK Population: This population will include all subjects who received at least one dose of ASN002 and have plasma concentration data.

The PD Population: This population will include all subjects who have at least one assessments of PD parameters

8.3 Statistical Analyses

8.3.1 General Approach

Continuous variables will be summarized in tables and will include the number of subjects, mean, standard deviation, median, minimum, and maximum. Categorical variables will be presented in tables as frequencies and percentages.

The primary efficacy analysis will be done using the mITT population and the PP population will be used as supportive analysis. All efficacy analyses will be performed using Mixed Model Repeated Measures (MMRM) analyses as primary analyses to take care of missing observations. Moreover, the analyses performed on observed case (i.e. without imputation of missing observations) will be done as sensitivity analyses.

Additional details regarding the efficacy and safety variable definitions, analyses strategy, control of the overall type 1 error, statistical justification, and techniques for handling missing values (e.g. for subjects who started prohibited medications) will be detailed in a SAP that will be prepared before the database is locked and any analyses are undertaken.

8.3.2 Efficacy Analyses

The primary efficacy endpoint will be analyzed using a repeated measures analysis of covariance on change-from-baseline variable to compare the time profile between treatments where the visit will be the time factor; and the stratification factors, treatment group, and interaction term for treatment-by-visit will be the fixed effects and the baseline value will be the covariate. An unstructured variance-covariance matrix will be used. Additional interaction terms will also be included in supportive statistical models and will be detailed in the SAP.

Sensitivity Analyses:

An analysis of covariance (ANCOVA) will be performed, where the absolute change from baseline at Week 12 will be the dependent variable; the treatment group and the stratification factors will be the fixed effects; and the baseline value will be the covariate. A supportive analysis with Site and Site-by-Treatment interaction included as fixed factors in addition to the other factors listed above will be performed in order to study the impact of site on efficacy.

A similar approach as for the primary endpoint will be done for all other continuous efficacy endpoints.

For categorical efficacy endpoints involving proportions of IGA, EASI and NRS (e.g. the proportion of subjects achieving at least a 2-grade reduction from baseline to clear (0) or almost clear (1) in Investigator's Global Assessment (IGA) at week 12), a Cochran Mantel Hansel test (CMH) controlling for the stratification variables will be performed.

Overall type 1 error control
For the primary endpoint of change-from-baseline in EASI at Week 12, a Bonferroni adjustment will be done to test the three comparisons of interest (40mg vs. Placebo, 60mg vs. Placebo and 80mg vs. Placebo) at alpha of 0.0167.

8.3.3 Safety Analyses

All safety data, including AEs and SAEs will be presented and tabulated according to Medical Dictionary for Regulatory Activities (MedDRA) classification. Descriptions of AEs will include the start date, the stop date (if it resolved), the severity and seriousness of the AE, the causality of the AE to study product, and the outcome. The focus in this protocol will be the prevalence of TEAEs and drug-related TEAEs.

Reported AEs will be summarized by the number of subjects reporting the events, as well as by System Organ Class, Preferred Term, severity, seriousness, and relationship to study product. For the summary of AEs by severity, each subject will be counted only once within a System Organ Class or a Preferred Term by using the AEs with the highest intensity within each category for each analysis. For the summary of AEs by relationship to study product, each subject will be counted only once within a System Organ Class or a Preferred Term by using the AEs with the greatest reported relationship within each category. For the summary of AEs by relationship to study product and severity, each subject will be counted only once within a System Organ Class or a Preferred Term by using (1) the greatest reported relationship followed by (2) the highest reported intensity.

All information pertaining to AEs noted during the study will be listed by subject, detailing verbatim, System Organ Class, Preferred Term, start date, stop date, intensity, outcome, and relationship to study product. The AE onset will also be shown relative (in number of days) to the day of study product administration. SAEs will be tabulated by treatment group, relationship to the test article, and a reference to the occurrence of the SAEs to the relative day of dosing.

Results from laboratory analyses, vital signs, ECGs, and physical examinations will be tabulated by treatment and visit using descriptive statistics. The value at each visit as well as the change from baseline will be presented descriptively.

Concomitant medications will be coded with the World Health Organization (WHO) Drug Dictionary and listed by subject. Summary of medication classes will also be tabulated.

No inferential statistics will be done on safety variables.

8.3.4 Pharmacokinetic Analyses

ASN002 concentration data will be listed per subject and summarized descriptively per dose.

Individual plasma concentration vs. actual time profiles for each subject and treatment, as well as the mean (±SD) plasma concentration vs. scheduled time profiles for each dose level, will be presented graphically.

8.3.5 Pharmacodynamic Analyses

A biomarker analysis will be performed on blood and biopsy samples collected to evaluate PD effects of ASN002 on inflammatory markers and cell populations. Biomarker levels will be compared to placebo adjusted change from baseline over time for each treatment group, and the parameters will be summarized by treatment group and overall using descriptive statistics.

8.3.6 Other Analyses

Descriptive summaries of baseline characteristics, including demographic data, prior concomitant therapy, and of subject disposition will be presented. In addition, a list of subjects who discontinued from the study will be provided

Protocol deviations will be summarized by treatment and category.

8.3.7 Planned Interim Analysis

No formal interim analyses are planned for this study. However, unblinded safety data will be generated and reviewed by the DSMB during the study.

9 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

9.1 Local Regulations/Declaration of Helsinki

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with ICH Tripartite Guideline for GCP and the applicable laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual.

9.2 Ethical Review

It is the understanding of the sponsor that this protocol (and any amendments) as well as appropriate consent procedures, will be reviewed and approved by an IRB/EC. This board must operate in accordance with the current federal regulations. For sites with a local ethics committee, a letter or certification of approval will be sent by the investigator to the sponsor (or CRO) before initiation of the study and also whenever subsequent modifications to the protocol are made.

9.3 Informed Consent Process

An Informed Consent Form describing in detail the study products, study procedures, and risks will be given to the subject, along with an assent form when required.

It is the responsibility of the investigator, or a person designated by the investigator (if acceptable by local regulation), to obtain written informed consent from each individual participating in this study, after adequate explanation of the aims, methods, objectives, and potential hazards of the study.

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be IRB/EC approved, and the subject will be asked to read and review the document. The investigator will explain the research study to the subject and answer any questions that may arise. A verbal explanation will be provided in terms suited to the subject's comprehension of the purposes, procedures, and potential risks of the study and of his or her rights as a research subject. Subjects will have the opportunity to carefully review the written consent form and ask questions prior to signing. The subjects should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate.

The subject will sign the informed consent document prior to any procedures being done specifically for the study. Subjects must be informed that participation is voluntary and that they may withdraw from the study at any time for any reason, without prejudice. A copy of the signed informed consent document will be given to the subjects for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the subject undergoes any study-specific procedures.

The rights and welfare of the subjects will be protected by emphasizing to them that the quality of

their medical care will not be adversely affected if they decline to participate in this study.

If new safety information results in significant changes in the risk/benefit assessment, or if any new information becomes available that may affect the willingness of a subject to continue to participate, the consent form should, if necessary, be reviewed and updated by the IRB/EC. All subjects (including those already being treated) should be informed of the new information, given a copy of the revised form, and asked to give their consent to continue in the study.

9.4 Study Discontinuation and Closure

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study subjects, investigators, the sponsor, and regulatory authorities. If the study is prematurely terminated or suspended, the principal investigators will promptly inform study subjects and the IRB/EC, and will provide the reason(s) for the termination or suspension. Study subjects will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension of the study include, but are not limited to the following:

- Determination of unexpected, significant, or unacceptable risk to subjects
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete or evaluable
- Scientific or corporate reasons

The study may resume once concerns about safety, protocol compliance, and data quality are addressed and satisfy the sponsor, IRB/EC, and applicable local regulations.

9.5 Confidentiality and Privacy

Subject confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor and their interventions. This confidentiality is extended to cover testing of biological samples in addition to the clinical information relating to subjects. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence.

The investigator must assure that the subjects' anonymity will be maintained and that subjects' identities are protected from unauthorized parties. On case report forms or other documents submitted to the sponsor, subjects should not be identified by their names, but by an identification code. The investigator should keep a subject enrollment log relating codes with the names of subjects. The investigator should maintain in strict confidence documents not for submission to the sponsor (e.g., subjects' written consent forms).

All research activities will be conducted in a setting as private as possible.

The study monitor, other authorized representatives of the sponsor, and representatives of the

IRB/EC, regulatory agencies, or pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the subjects in this study. The clinical study site will permit access to such records.

The study subject's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the applicable legal or regulatory requirements, the reviewing IRB/EC, institutional policies, or sponsor requirements.

9.6 Clinical Monitoring

Clinical site monitoring will be conducted to ensure that the rights and well-being of trial subjects are protected; that the reported trial data are accurate, complete, and verifiable; and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), ICH GCP guidelines, and with applicable regulatory requirement(s). Details of clinical site monitoring will be documented in a Monitoring Plan.

9.7 Quality Assurance and Quality Control

Each clinical site will perform internal quality management of study conduct, data and biological specimen collection, documentation, and completion.

Quality control (QC) procedures will be implemented beginning with the data entry system, and data QC checks, which will be run on the database, will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

During the study, the sponsor or its representative will conduct monitoring visits at regular intervals. The monitoring visits will be conducted to ensure protocol adherence, quality of data, accuracy of entries on the eCRFs, study product accountability, compliance with regulatory requirements, and continued adequacy of the investigational site and its facilities.

The site may be audited, monitored, or inspected by a quality assurance officer named by the sponsor, by the IRB/EC, and/or by the regulatory authorities. The investigator will be given notice before an audit occurs and will be expected to cooperate with any audit and provide assistance and documentation (including source data) as requested. The investigational site will provide direct access to all trial-related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor and inspection by local and regulatory authorities.

9.8 Data Handling and Record Keeping

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be

classified into two separate categories: investigator's study files and subject clinical source documents.

The investigator must maintain source documents for each subject in the study. These source documents will consist of case and visit notes (clinical medical records) containing demographic and medical information and the results of any tests or assessments. All information on the eCRFs must be traceable to the source documents in the subject's file. Data not requiring a written or electronic record will be defined before study start and will be recorded directly on the eCRFs, which will be documented as being the source data.

The records should be retained by the investigator according to ICH guidelines, local regulations, or as specified in the Clinical Trial Agreement, whichever retention period is longer.

Subject data will be entered by site personnel using Medrio, a web-based EDC and reporting system. This application will be set up for remote entry. Medrio Inc. is the developer and owner of Medrio. The EDC software has been fully validated and conforms to Title 21 of the Code of Federal Regulations, Part 11 requirements. Investigator site staff will not be given access to the EDC system until they have been fully trained. Designated investigator staff will enter the data required by the protocol into the eCRFs using this web-based application. Automatic validation programs check for data discrepancies in the eCRFs and, by generating appropriate error messages, allow modification or verification of the entered data by the investigator staff before confirming the data. The investigator must certify that the data are complete and accurate by applying an electronic signature to the eCRFs.

The data collected will be encoded and stored electronically in a database system. Validated data may subsequently be transferred to the sponsor.

9.9 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol requirements. The noncompliance may be either on the part of the subject, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

Protocol deviations must be sent to the reviewing IRB/EC as per the IRB/EC requirements.

9.10 Publication Policy

The publication policy will be addressed in the Research and Financial Agreement, and all details outlined in the agreement will apply to this protocol. The trial will be registered on ClinicalTrials.Gov prior to the first subject being dosed.

10 REFERENCES

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APPENDIX A: Diagnostic Criteria for Atopic Dermatitis

Per Inclusion Criterion 2, a subject is to have a clinical diagnosis of atopic dermatitis according to the criteria of Hanifin and Rajka.[25] The criteria are as follows:

Major Criteria (must have at least three)

- Pruritus
- Typical morphology and distribution:
  - Adults: flexural lichenification or linearity
  - Children and infants: involvement of facial and extensor surfaces
- Chronic or chronically relapsing dermatitis
- Personal or family history of atopy (asthma, allergic rhinitis, atopic dermatitis)

Minor Criteria (must have at least three)

- Xerosis
- Ichthyosis/keratosis pilaris/palmar hyperlinearity
- Immediate (Type 1) skin test reactivity
- Elevated serum IgE
- Early age at onset
- Tendency to skin infections (*Staphylococcus aureus*, herpes simplex)/impaired cellular immunity
- Tendency to nonspecific hand/foot dermatitis
- Nipple eczema
- Cheilitis
- Recurrent conjunctivitis
- Dennie-Morgan infraorbital fold
- Keratoconus
- Anterior subcapsular cataracts
- Orbital darkening
- Facial pallor/erythema
- Pityriasis alba
- Anterior neck folds
- Itch when sweating
- Intolerance to wool and lipid solvents
- Perifollicular accentuation
- Food intolerance
- Course influenced by environmental/emotional factors
- White dermographism/delayed blanch

APPENDIX B: Eczema Area and Severity Index

Four anatomic sites—head, upper extremities, trunk, and lower extremities—are assessed for erythema, induration/infiltration (papules), excoriation, and lichenification as seen on the day of the examination. The severity of each sign is assessed using a 4-point scale (half steps **are** allowed):

- 0 = none
- 1 = mild
- 2 = moderate
- 3 = severe

The area affected by atopic dermatitis within a given anatomic site is estimated as a percentage of the total area of that anatomic site and assigned a numerical value according to the degree of atopic dermatitis involvement as follows:

- 0 = no involvement
- 1 = <10%
- 2 = 10% to <30%
- 3 = 30% to <50%
- 4 = 50% to <70%
- 5 = 70% to <90%
- 6 = 90% to 100%

The EASI score is obtained by using the formula below:

$$EASI = 0.1\,(E_h + I_h + Ex_h + L_h)\,A_h + 0.2\,(E_u + I_u + Ex_u + L_u)\,A_u + 0.3\,(E_t + I_t + Ex_t + L_t)\,A_t + 0.4\,(E_l + I_l + Ex_l + L_l)\,A_l$$

Where E, I, E*x*, L, and A denote erythema, induration, excoriation, lichenification and area, respectively, and h, u, t, and l denote head, upper extremities, trunk, and lower extremities, respectively.

APPENDIX C: vIGA-AD™

Validated Investigator Global Assessment scale for Atopic Dermatitis

vIGA-AD™

Instructions:

The IGA score is selected using the descriptors below that best describe the overall appearance of the lesions at a given time point. It is not necessary that all characteristics under Morphological Description be present.

Score	Morphological Description
0 – Clear	No inflammatory signs of atopic dermatitis (no erythema, no induration/papulation, no lichenification, no oozing/crusting). Post-inflammatory hyperpigmentation and/or hypopigmentation may be present.
1 – Almost clear	Barely perceptible erythema, barely perceptible induration/papulation, and/or minimal lichenification. No oozing or crusting.
2 – Mild	Slight but definite erythema (pink), slight but definite induration/papulation, and/or slight but definite lichenification. No oozing or crusting.
3 – Moderate	Clearly perceptible erythema (dull red), clearly perceptible induration/papulation, and/or clearly perceptible lichenification. Oozing and crusting may be present.
4 – Severe	Marked erythema (deep or bright red), marked induration/papulation, and/or marked lichenification. Disease is widespread in extent. Oozing or crusting may be present.

Notes:

1. In indeterminate cases, please use extent to differentiate between scores.

For example:

- *Patient with marked erythema (deep or bright red), marked papulation and/or marked lichenification that is limited in extent, will be considered "3 – Moderate".*

2. Excoriations should not be considered when assessing disease severity.

APPENDIX D: Scoring Atopic Dermatitis - SCORAD

Six items (erythema, edema/papulation, oozing/crusts, excoriation, lichenification, and dryness) are selected to evaluate the atopic dermatitis severity. The intensity of each item is graded using a 4-point scale (half steps **not** allowed):

- 0 = absence
- 1 = mild
- 2 = moderate
- 3 = severe

The area chosen for grading must be representative (average intensity) for each item. The individual intensity ratings for each item will then be added (ranging from 0-18) and multiplied by 3.5, giving a maximal score of 63.

The overall BSA affected by atopic dermatitis is evaluated (from 0% to 100%) and divided by 5. One subject's palm represents 1% of his or her total BSA. The maximum is 20.

Subjective items include loss of sleep and the occurrence of pruritus. These are evaluated by asking subjects to indicate on the 10-cm scale (0-10) of the assessment form the point corresponding to the average value for the last 3 days/nights. The combined maximum score of these two is 20.

The sum of the measures above represents the SCORAD, which can vary from 0 to 103. If the subjective scores of pruritus and loss of sleep are excluded, the SCORAD becomes objective SCORAD (score range 0-83).

APPENDIX E: Patient-Oriented Eczema Measure

5-D Pruritus Scale

1. **Duration**: During the last 2 weeks, how many hours a day have you been itching?

Less than 6hrs/day	6-12 hrs/day	12-18 hrs/day	18-23 hrs/day	All day
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

2. **Degree**: Please rate the intensity of your itching over the past 2 weeks

Not present	Mild	Moderate	Severe	Unbearable
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

3. **Direction**: Over the past 2 weeks has your itching gotten better or worse compared to the previous month?

Completely resolved	Much better, but still present	Little bit better, but still present	Unchanged	Getting worse
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

4. **Disability**: Rate the impact of your itching on the following activities over the last 2 weeks

	Never affects sleep	Occasionally delays falling asleep	Frequently delays falling asleep	Delays falling asleep and occasionally wakes me up at night	Delays falling asleep and frequently wakes me up at night
Sleep	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

	N/A	Never affects this activity	Rarely affects this activity	Occasionally affects this activity	Frequently affects this activity	Always affects this activity
Leisure/Social	☐	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Housework/ Errands	☐	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Work/School	☐	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

5. **Distribution:** Mark whether itching has been present in the following parts of your body over the last 2 weeks. If a body part is not listed, choose the one that is closest anatomically.

	Present		Present
Head/Scalp	☐	Soles	☐
Face	☐	Palms	☐
Chest	☐	Tops of Hands/Fingers	☐
Abdomen	☐	Forearms	☐
Back	☐	Upper Arms	☐
Buttocks	☐	Points of Contact w/ Clothing	
Thighs	☐	(e.g waistband, undergarment)	☐
Lower legs	☐	Groin	☐
Tops of Feet/Toes	☐		

APPENDIX F: Patient-Oriented Eczema Measure

Subject ID #: ___ ___ - ___ ___ ___ Subject Initials: ___ ___ ___

Visit Day: _____ Visit Date (dd-mmm-yyyy):_____

Please circle one response for each of the seven questions below about your eczema. Please leave blank any questions you feel unable to answer.

1. **Over the last week, on how many days has your skin been itchy because of your eczema?**

No days 1-2 days 3-4 days 5-6 days Every day

2. **Over the last week, on how many nights has your sleep been disturbed because of your eczema?**

No days 1-2 days 3-4 days 5-6 days Every day

3. **Over the last week, on how many days has your skin been bleeding because of your eczema?**

No days 1-2 days 3-4 days 5-6 days Every day

4. **Over the last week, on how many days has your skin been weeping or oozing clear fluid because of your eczema?**

No days 1-2 days 3-4 days 5-6 days Every day

5. **Over the last week, on how many days has your skin been cracked because of your eczema?**

No days 1-2 days 3-4 days 5-6 days Every day

6. **Over the last week, on how many days has your skin been flaking off because of your eczema?**

No days 1-2 days 3-4 days 5-6 days Every day

7. **Over the last week, on how many days has your skin felt dry or rough because of your eczema?**

No days 1-2 days 3-4 days 5-6 days Every day

APPENDIX G: Dermatology Life Quality Index

Subject ID #: ___ ___ - ___ ___ ___ Subject Initials: ___ ___ ___

Visit Day: _____ Visit Date (dd-mmm-yyyy):_____

The aim of this questionnaire is to measure how much your skin problem has affected your life OVER THE LAST WEEK. Please check one box for each question.

1.	Over the last week, how **itchy**, **sore**, **painful** or **stinging** has your skin been?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	
2.	Over the last week, how **embarrassed** or **self conscious** have you been because of your skin?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	
3.	Over the last week, how much has your skin interfered with you going **shopping** or looking after your **home** or **yard?**	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
4.	Over the last week, how much has your skin influenced the **clothes** you wear?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
5.	Over the last week, how much has your skin affected any **social** or **leisure** activities?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
6.	Over the last week, how much has your skin made it difficult for you to do any **sport**?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
7.	Over the last week, has your skin prevented you from **working** or **studying**?	Yes No	☐ ☐	Not relevant ☐
	If "No," over the last week how much has your skin been a problem at **work** or **studying**?	A lot A little Not at all	☐ ☐ ☐	

8.	Over the last week, how much has your skin created problems with your **partner** or any of your **close friends** or **relatives**?	Very much A lot A little Not at all	□ □ □ □	 Not relevant □
9.	Over the last week, how much has your skin caused any **sexual difficulties**?	Very much A lot A little Not at all	□ □ □ □	 Not relevant □
10.	Over the last week, how much of a problem has the **treatment** for your skin been, for example by making your home messy, or by taking up time?	Very much A lot A little Not at all	□ □ □ □	 Not relevant □

Please check you have answered EVERY question. Thank you.